UNCLASSIFIED

AD NUMBER

ADB259035

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; Sep 99. Other requests shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott St., Fort Detrick, MD 21702-5012.

AUTHORITY

USAMRMC ltr, 26 Aug 2002

THIS PAGE IS UNCLASSIFIED

AD_____

Award Number: DAMD17-96-1-6294

TITLE: Stress and Immunity Breast Cancer Project

PRINCIPAL INVESTIGATOR: Barbara L. Andersen, Ph.D.

CONTRACTING ORGANIZATION: Ohio State University Research Foundation
Columbus, OH 43210-1063

REPORT DATE: September 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Distribution authorized to U.S. Government agencies only (proprietary information, Sep 99). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

DTIC QUALITY INSPECTED 4

20001027 012

NOTICE

USING GOVERNMENT DRAWINGS, SPECIFICATIONS, OR OTHER DATA INCLUDED IN THIS DOCUMENT FOR ANY PURPOSE OTHER THAN GOVERNMENT PROCUREMENT DOES NOT IN ANY WAY OBLIGATE THE U.S. GOVERNMENT. THE FACT THAT THE GOVERNMENT FORMULATED OR SUPPLIED THE DRAWINGS, SPECIFICATIONS, OR OTHER DATA DOES NOT LICENSE THE HOLDER OR ANY OTHER PERSON OR CORPORATION; OR CONVEY ANY RIGHTS OR PERMISSION TO MANUFACTURE, USE, OR SELL ANY PATENTED INVENTION THAT MAY RELATE TO THEM.

LIMITED RIGHTS LEGEND

Award Number: DAMD17-96-1-6294
Organization: Ohio State University Research Foundation

Those portions of the technical data contained in this report marked as limited rights data shall not, without the written permission of the above contractor, be (a) released or disclosed outside the government, (b) used by the Government for manufacture or, in the case of computer software documentation, for preparing the same or similar computer software, or (c) used by a party other than the Government, except that the Government may release or disclose technical data to persons outside the Government, or permit the use of technical data by such persons, if (i) such release, disclosure, or use is necessary for emergency repair or overhaul or (ii) is a release or disclosure of technical data (other than detailed manufacturing or process data) to, or use of such data by, a foreign government that is in the interest of the Government and is required for evaluational or informational purposes, provided in either case that such release, disclosure or use is made subject to a prohibition that the person to whom the data is released or disclosed may not further use, release or disclose such data, and the contractor or subcontractor or subcontractor asserting the restriction is notified of such release, disclosure or use. This legend, together with the indications of the portions of this data which are subject to such limitations, shall be included on any reproduction hereof which includes any part of the portions subject to such limitations.

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION.

[illegible signature] 10/18/00

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1999	Annual (15 Aug 98 -14 Aug 99)

4. TITLE AND SUBTITLE
Stress and Immunity Breast Cancer Project

5. FUNDING NUMBERS
DAMD17-96-1-6294

6. AUTHOR(S)
Barbara L. Andersen, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Ohio State University Research Foundation
Columbus, OH 43210-1063

E-MAIL:
andersen.1@osu.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (proprietary information, Sep 99). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

A biobehavioral model of cancer stress and disease course has been proposed (see Andersen, Kiecolt-Glaser, & Glaser, 1994). We are testing the model with a clinical trial: 235 women with stage II or III breast cancer who have been diagnosed and recently surgically treated are randomized between two conditions: (1) assessment and intervention, or (2) assessment only (control). In addition to documenting the quality of life benefits of a psychological intervention, this study provides an experimental test of the psychological and behavioral variables which may influence health outcomes directly. Further, we test specific mechanisms - alteration in immune and endocrine functions - to achieve beneficial health effects for women with breast cancer.

Data from the project indicate that psychological stress following diagnosis has a down regulating effect on immunity (Andersen et al., 1998). Psychological stress is also instrumental in increasing a woman's risk for depressive symptoms following definitive surgery (Golden-Kreutz et al., under review), and stress due to breast cancer surgery produces sexual and body image difficulties (Yurek et al, in press). Importantly, the psychological intervention results in significantly fewer depressive symptoms, lower levels of endocrine (cortisol), and higher mucin 1 antibody responses (Andersen et al., under review).

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer 2. psychological 3. stress 4. immunity 5. quality of life	138
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Limited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

___ Where copyrighted material is quoted, permission has been obtained to use such material.

___ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

___ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

X For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Barbara J. Anderson 8/20/99

PI - Signature Date

Table of Contents

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment for regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36. (Appendix A)

Andersen, B.L., Golden-Kreutz, D.M., McKolanis, J. , Malarkey, W., Farrar, W.B., DeLamatre, M., & Finn, O. J. (Under review). Recovery of tumor antigen (MUC1) specific antibody following successful stress reduction in breast cancer patients randomized to a psychological intervention in addition to standard therapy. (Appendix B)

Golden-Kreutz, D.M., Courtney, M.E., & Andersen, B.L. (Under review). Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment. (Appendix C)

Yurek, D., Farrar, W., & Andersen, B.L. (Accepted pending revisions). Breast cancer surgery: Comparing surgical groups and determining individual differences in post operative sexuality and body change stress. *Journal of Consulting and Clinical Psychology.* (See Appendix D).

INTRODUCTION

We have proposed a biobehavioral model of cancer stress and disease course (see Andersen, Kiecolt-Glaser, & Glaser, 1994, for a full discussion). The model identifies the psychological and behavioral factors and the biologic mechanisms by which health outcomes and cancer progression might be influenced. This model provides the conceptual basis for the proposed research . The present study is a randomized clinical trial testing the model. 235 women with stage II or III breast cancer who have been diagnosed and recently surgically treated are randomized between two conditions: (1) assessment and intervention, or (2) assessment only (control). In addition to documenting the quality of life benefits of a psychological intervention, this study provides an experimental test of the psychological and behavioral variables which may influence health outcomes directly. Further, we test specific mechanisms--alteration in immune and endocrine functions--to achieve beneficial health effects for women with breast cancer.

BODY

Army funding in 1996 enabled this large, important effort to continue beyond the pilot phase. Full funding has enabled us to move aggressively ahead on subject accrual, complete the backlog of previously unfunded tasks, and, importantly, expand the biologic aspect of the project to include a breast cancer specific immune assay mucin-1 (MUC-1) and an endocrine panel of measures (e.g. serum cortisol, catecholamines, prolactin, growth hormone). Three types of preliminary data are provided, per the statement of work: Task 1 (Recruitment), Task 2 (Intervention Groups), Task 3 and 4 (Data Collection and Analysis).

Task 1: Recruitment and Accrual

Eligible women are newly diagnosed and/or recently treated (i.e. < 3 months post surgery) women with Stage II or III invasive breast cancer who are ≥ 20 years of age. Following accrual, women are randomized and followed according to the time line indicated below in Table 1. Considering accrual thus far, "up front" refusal rates are running 38%, and 12 month dropout rate is extremely low, 6.5%. The literature suggests that refusal rates in psychosocial intervention studies have ranged from 10 to 25% (Andersen, 1992). In considering the drop out rate, studies of low and moderate risk patients (i.e. Stage I - III: Andersen, 1992) were considered. The literature suggests that dropout rates range from 9% to 27% for the studies which have provided data for initial to 12 month assessments. Thus, the actual rates in this study are extremely good. Also, we have conducted analyses examining the potential for biases between the groups on sociodemographic, disease or health variables, and current analyses find no significant group differences on any variable at the initial assessment between the study arms.

Table 1: Schematic diagram of the research design for subjects across the 4 years of study participation.

	YEAR 1				YEARS 2-4	
	Dx./Ca. Trt	Follow up (months)			Cont. Follow up (months)	
Grp	0	4	8	12	6	12
1	x----------Inten------x----Maintenance---x--Maintenance--x				x	x
2	x----------None-----x--------None-------x-------None-----x				x	x

Note: *Dx.* = Cancer diagnosis and *Ca.Trt.* = Beginning of initial cancer treatment; Inten(sive) = Weekly (x18) intervention sessions with reliability/validity checks on intervention integrity; Maintenance = Monthly (x8) intervention sessions with reliability/validity checks; *x* = Psychological, health behavior, compliance, and immune and endocrine assessments and disease endpoints.

Below in Table 2 is a tally for the accrual rate and resulting numbers of psychological/medical/immune assessments for grant years 1-4. This summary is based on an annual projected rate of 60 potential subjects approached for recruitment per year, 45 Ss actually recruited and assessed per year. Per subject, there are 4 assessments during year 1 of participation (45 Ss x 4 = 180) and 2 assessments/year for years 2-4 (assuming 45 Ss x 2 = 90 for years 2 and 3) of participation. Rates designated with an asterisk (*) are projections. There are approximately 200 Ss accrued thus far.

Table 2: Accrual: Actual rate and projections* for remainder of grant period.

Grant year	Accrual	Assessments by Accrual Year					Assessment Summary
		Pilot	1	2	3	4	N/year
Pilot	45	180	___	___	___	___	180
1st year	45	90	180	___	___	___	270
2nd year	45	90	90	180	___	___	360*
3rd year	45	90	90	90	180	___	450
4th year	45*	90*	90*	90*	90*	180*	540*

Task 2: Intervention Group

Nine cohorts of intervention groups have been conducted. There is presently a 4.2% drop out rate in the intervention arm. Because this rate is so low, it is difficult to single out particular reasons for drop out, however clinical data would suggest that women with prior psychiatric histories (e.g. major depression, agorophobia) are at greatest risk, and we are vigorously attending to these conditions to meet the needs of these women and retain them in the study even though they do not complete the intervention. We analyze data according intention to treat.

Task 3 and 4: Data Collection and Analysis

Previous relevant findings:

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36. (See Appendix A).

We examined the relationship between stress and several aspects of the cellular immune response in the context of the diagnosis of breast cancer and the post surgery period. Women (N = 116) recently surgically treated for Stage II (70%) or III (30%) invasive breast cancer participated. Prior to beginning adjuvant therapy, all completed a validated questionnaire assessing stress about the cancer experience and provided a 60cc blood sample. A panel of natural killer (NK) cell and T-cell assays were conducted: 1) NK cell lysis; 2) the response of NK cells to recombinant gamma interferon (rIFN-γ) and recombinant interleukin-2 (rIL-2); 3) blastogenic response of peripheral blood leukocytes (PBLs) to phytohemagglutinin A (PHA) and concanavalin A (ConA) and the proliferative response of PBLs to a monoclonal antibody (MAb) to the t-cell receptor (T3).

Multiple regression models were used to test the contribution of psychological stress in predicting immune function. We hypothesized a negative relationship between stress and immunity, and expected this relationship to be replicated between assays and within a single assay [i.e. replicated across effector to target (E:T) cell ratios for

NK cell lysis, for example]. All regression equations controlled for variables which might also be expected to exert short or long term effects on these responses, such as age, stage of disease, and length of time of surgical recovery, and ruled out other potentially confounding variables (e.g. nutritional status) that might also be influential. These controls reduced the plausibly of alternative, rival hypotheses for the findings.

Significant effects were found and replicated between and within assays, including the following: 1) stress significantly ($p < .05$) predicted NK cell lysis; 2) stress significantly ($p < .01$) predicted the response of NK cells to rIFN-γ; 3) stress significantly predicted the response of PBLs to ConA ($p < .05$) and PHA ($p < .05$), and the proliferative response to the T3 MAb ($p < .05$). The cells from 62% of the sample did not respond to rIL-2, but stress was not a factor in predicting the response for the remainder of the sample (38%). The data show that the physiologic effects of stress inhibited a panel of cellular immune responses, cancer relevant NK cell cytotoxicity and T cell responses. Our additional data accrued since the publication of these findings confirm the reliability of these observations.

Important findings of the current year (1998-1999)

Andersen, B.L., Golden-Kreutz, D.M., McKolanis, J. , Malarkey, W., Farrar, W.B., DeLamatre, M., & Finn, O. J. (Under review). Recovery of tumor antigen (MUC1) specific antibody following successful stress reduction in breast cancer patients randomized to a psychological intervention in addition to standard therapy. (See Appendix B).

Background: The body's response to stress involves the autonomic, endocrine, and immune systems in addition to psychological and behavioral responses. Our previous studies with women with breast cancer who were assessed during the post surgery recovery period found that high levels of psychological stress were related to the down regulation of a panel of cellular immune responses, including NK cell function (i.e. lytic activity, response to rIFN-γ) and T cell function (i.e., proliferation and blastogenesis) (Andersen et al., 1998). Our intent was to experimentally determine if a psychological intervention designed to reduce cancer related stress and enhance quality of life could also influence biologic responses, that is, to down regulate endocrine stress responses and up-regulate immune responses. Importantly, the test was conducted with an anti-tumor immune response against a breast cancer antigen, MUC1. The assessment of anti-MUC1 antibody could serve as a surrogate marker of an overall anti-tumor response in the patient. *Method:* We studied 116 women who had been diagnosed and surgically treated for Stage II or III invasive breast cancer. Before beginning their adjuvant cancer therapy, each woman complete a validated questionnaire assessing depressive symptoms and a 60-ml blood sample was drawn for plasma cortisol and MUC1 specific antibody assays. Patients were then randomized between Intervention and assessment vs. Assessment only study arms. The 12 month psychological/behavioral intervention was designed to reduce stress and improve quality of life. Monitoring of all patients was repeated at 4, 8, and 12 months. *Results:* We found that women receiving the intervention showed significant 1) lowering of stress as indexed by serum cortisol, 2) fewer depressive symptoms, and 3) prompt recovery and maintenance of anti-MUC1 antibody response, in contrast to the responses of the patients in the Assessment only study arm. *Conclusion:* To our knowledge, these are the first experimental data showing a convergence of psychological, endocrine, and immune effects with a psychological/behavioral intervention, and, importantly, the intervention enhanced a breast cancer relevant immune response. Continued follow up is needed to determine the health consequences of these effects and their biobehavioral mechanisms.

Golden-Kreutz, D.M., Courtney, M.E., & Andersen, B.L. (Under review). Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment.

The relationship of objective stressors (life events) and subjective (perceived) stress to depressive symptoms was examined. These relationships were examined using a clinically relevant paradigm, stressed individuals who were vulnerable to the experience of depressive symptoms, namely women recently diagnosed and surgically treated for breast cancer. Analyses controlled for alternative hypotheses including: sociodemographic, disease, and personality factors. Using Hierarchical Multiple Regression, 51% of the variance in depressive symptoms was predicted, accounted for by the control variables (race, neuroticism), objective stressors (major financial difficulty

and major conflict with children/grandchildren), subjective event stress (cancer stress; IES), and subjective global stress (PSS-10). An examination of the squared semipartial correlations indicated that perceived stress (10%), cancer stress (8%), and race (1%) accounted for significant unique variance in the final model. While "stress" measures are correlated, these findings indicate that subjective measures of stress were uniquely better predictors of depressive symptoms than objective measures. Further, a global perception of stress was a stronger predictor than perceived stress for a specific event. Implications for the use of such measures with stressed populations, who are often vulnerable to other comorbid difficulties such as depression, are discussed.

Yurek, D., Farrar, W., & Andersen, B.L. (Accepted pending revisions). Breast cancer surgery: Comparing surgical groups and determining individual differences in post operative sexuality and body change stress. *Journal of Consulting and Clinical Psychology.* (See Appendix D).

Women diagnosed and surgically treated for regional breast cancer (N = 190) were studied in the early post surgical period to determine the sexual and body change sequelae for women receiving modified radical mastectomy with breast reconstruction (MRMw/R) in comparison to the sequelae for women receiving breast conserving therapy (BCT) or modified radical mastectomy without breast reconstruction (MRM). The sexuality pattern for women receiving reconstructive surgery (MRMw/R) was one that was significantly different--with lower rates of activity and fewer signs of sexual responsiveness--than that for women in either of the other groups. Significantly higher levels of traumatic stress and situational distress regarding the breast changes were reported by the women receiving a modified radical mastectomy, whether or not they had undergone reconstruction, in contrast to the women treated with BCT. Finally, regression analyses, which controlled for menopausal status, prior behavior, and extent of disease and treatment, revealed that individual differences in sexual self schema were related to both sexual and body change stress outcomes.

KEY RESEARCH ACCOMPLISHMENTS

- Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36.

- Yurek, D., Farrar, W., & Andersen, B.L. (Accepted pending revisions). Breast cancer surgery: Comparing surgical groups and determining individual differences in post operative sexuality and body change stress. *Journal of Consulting and Clinical Psychology.*

- Andersen, B.L., Golden-Kreutz, D.M., McKolanis, J. , Malarkey, W., Farrar, W.B., DeLamatre, M., & Finn, O. J. (Under review). Recovery of tumor antigen (MUC1) specific antibody following successful stress reduction in breast cancer patients randomized to a psychological intervention in addition to standard therapy.

REPORTABLE OUTCOMES

Manuscripts, abstracts and presentations

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36.

Andersen, B.L. (1998). Psychology's science in responding to the challenge of cancer: Biobehavioral perspectives. *Psychological Science Agenda, 11 (1),* 14-15.

Andersen, B.L. (1998). Cancer. In H.S. Friedman (Ed.), *Encyclopedia of Mental Health, Vol.1.* San Diego: Academic Press. (pp.373-378).

Andersen, B.L., & Golden-Kreutz, D. (1998). Cancer. In A.S. Bellack & M. Hersen (Eds.), *Comprehensive clinical psychology*. Pergamon. (pp 217-236).

Andersen, B.L. (1998). Breast cancer: Biobehavioral aspects. In E.A. Blechman and K. Brownell (Eds.), *Behavioral medicine for women: A comprehensive handbook* (pp. 570-576. Guilford Publications.

Cyranowski, J.C., Aarestad, S.L., & Andersen, B.L. (1999). The role of sexual self schemas in a diathesis-stress model of sexual dysfunction. *Applied and Preventive Psychology, 8 (3),* 217-228.

Andersen, B.L. (1999). Surviving cancer: The importance of sexual self concept. *Medical and Pediatric Oncology, 33 (1),* 15-23.

Andersen, B.L., & Golden-Kreutz, D. (in press). Cancer. In A. Baum, C. McManus, S. Newman, J. Weinman, & R. West. (Eds.), *Cambridge handbook of psychology, health, and medicine*. Cambridge University Press.

Andersen, B.L., Golden-Kreutz, D., DiLillo, V. (in press). Cancer. In A.E. Kazdin (Ed.), *Encyclopedia of psychology*. American Psychological Association Press.

Andersen, B.L., W.B. Farrar, & L.J. Copeland. (in press). Cancer. In E.Palace (Ed.), *Women's health: A behavioral medicine approach.* Oxford University Press.

Andersen, B.L., Golden-Kreutz, D., & DiLillo, V. (in press). Cancer. In A. Baum, T. Revenson, & J. Singer (Eds.), *Handbook of health psychology.* Erlbaum.

Andersen, B.L. (in press). Sexuality and cancer. In G.P. Murphy, W. Lawrence, Jr., and R.E. Lenhard, Jr. (Eds.) *American Cancer Society textbook of clinical oncology, 3rd edition.* Atlanta: American Cancer Society, Inc.

Stress, immunity and breast cancer. In C. Johansen (Chair), Stressors and stress reduction interventions in cancer patients: Effects on adjustment, health and immunity. International Congress of Behavioral Medicine, Copenhagen, Denmark, August 1998.

Biobehavioral aspects of cancer recurrence. In M.A. Andrykowski and A. Baum (Chairs), Presidential Miniconvention on Cancer--State of the art research programs in cancer. American Psychological Association Annual Meeting, Boston, August 1999.

Biobehavioral aspects of cancer: psychological, behavioral and biological responses. (Invited Address, Divisions 38 and 47). American Psychological Association Annual Meeting, Boston, August 1999.

Patents and licenses applied for and/or issued: NA

Degrees obtained that are supported by this award:

Postdoctoral students

Deanna Golden-Kreutz, Ph.D., 1996-1999
Vicki DiLillo, Ph.D., 1997-1998
Sharla Wells, Ph.D., 1999-present

Dissertation:

Deborah Yurek, Ph.D., (1997)
Susan Aarestad, Ph.D. (1999)

MA/MS thesis:

Beth Putz, 1996
Elizabeth Bromet, 1996
Derek Espindle, 1997
Georita Frierson, 1999
Larissa Demshuk, in progress
Heather Lawrence, in progress
Lisa Thornton, in progress

Development of cell lines, tissue or serum repositories: NA

Informatics such as data bases and animal models, etc.: NA

Funding applied for based on work supported by this award:

Walther Cancer Institute; 8/97-8/99. B. Andersen (PI): Biobehavioral aspects of cancer recurrence. Total costs: $120,000.

Dana Foundation; 1/1/00-12/31/01. B. Andersen (co-PI) and W. Carson (co-PI): Mechanisms of stress-related effects on host immune responses in breast cancer. Total costs: $100,000.

Employment or research opportunities applied for and or received on experiences/training supported by this award:

DiLillo, V., Ph.D. (1998). Assistant Professor, Department of Psychiatry, University of Alabama-Birmingham.

Deanna Golden-Kreutz, Ph.D. (1997-99). Postdoctoral award, Army Research and Development Command.

CONCLUSIONS

To summarize, we view stress, QoL, health behaviors, and compliance as the major factors in a conceptual model of adjustment to the cancer stressor. Also part of the model are the physiological systems--the endocrine and immune systems--which may be important ones for moderating the effects of stress on disease processes. This experimental test of the model is a "simple" experimental design--a comparison of treatment vs. no treatment. This was a strategic next step for the field as it provides cause--effect data for the presence of an intervention producing enhanced psychological and behavioral outcomes, immune responses, and health effects. In addition to the biobehavioral model, the specific design of the intervention, with intensive and maintenance phases, is novel. Important, novel findings have already emerged from the research.

We have documented that the psychological stress of cancer diagnosis and breast cancer surgery produces important psychological and immune effects. The stress is instrumental in increasing a woman's risk for experiencing depressive symptoms (Golden Kreutz et al., under review) and body image and sexual distress (Yurek, Farrar, & Andersen, in press). Stress is also instrumental in producing a broad band down regulation of womens' immune responses (Andersen et al., 1998). We found NK cell function and T cell proliferation and blastogenesis is impaired.

We now have data to document impressive biobehavioral--psychological, behavioral, endocrine, and immune effects--of the intervention. We found that women receiving the intervention showed significantly 1) fewer depressive symptoms; 2) greater compliance with cancer chemotherapy; 3) lower stress as indexed by serum cortisol; and, 4) greater recovery and maintenance of anti-MUC1 antibody response, in contrast to the responses of the patients in the Assessment only study arm. To our knowledge, these are the first experimental data showing a convergence of psychological, behavioral, endocrine, and immune effects with a psychological/behavioral intervention, and, importantly, the intervention enhanced a breast cancer relevant immune response.

REFERENCES

Andersen, B.L. (1998). Psychology's science in responding to the challenge of cancer: Biobehavioral perspectives. *Psychological Science Agenda, 11 (1),* 14-15.

Andersen, B.L. (1998). Cancer. In H.S. Friedman (Ed.), *Encyclopedia of Mental Health, Vol.1.* San Diego: Academic Press. (pp.373-378).

Andersen, B.L. (1998). Breast cancer: Biobehavioral aspects. In E.A. Blechman and K. Brownell (Eds.), *Behavioral medicine for women: A comprehensive handbook* (pp. 570-576. Guilford Publications.

Andersen, B.L. (1999). Surviving cancer: The importance of sexual self concept. *Medical and Pediatric Oncology, 33 (1),* 15-23.

Andersen, B.L. (in press). Sexuality and cancer. In G.P. Murphy, W. Lawrence, Jr., and R.E. Lenhard, Jr. (Eds.) *American Cancer Society textbook of clinical oncology, 3rd edition.* Atlanta: American Cancer Society, Inc.

Andersen, B.L., W.B. Farrar, & L.J. Copeland. (in press). Cancer. In E.Palace (Ed.), *Women's health: A behavioral medicine approach.* Oxford University Press.

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36.

Andersen, B.L., & Golden-Kreutz, D. (1998). Cancer. In A.S. Bellack & M. Hersen (Eds.), *Comprehensive clinical psychology.* Pergamon. (pp 217-236).

Andersen, B.L., & Golden-Kreutz, D. (in press). Cancer. In A. Baum, C. McManus, S. Newman, J. Weinman, & R. West. (Eds.), *Cambridge handbook of psychology, health, and medicine.* Cambridge University Press.

Andersen, B.L., Golden-Kreutz, D., DiLillo, V. (in press). Cancer. In A.E. Kazdin (Ed.), *Encyclopedia of psychology.* American Psychological Association Press.

Andersen, B.L., Golden-Kreutz, D., & DiLillo, V. (in press). Cancer. In A. Baum, T. Revenson, & J. Singer (Eds.), *Handbook of health psychology.* Erlbaum.

Andersen, B.L., Golden-Kreutz, D.M., McKolanis, J. , Malarkey, W., Farrar, W.B., DeLamatre, M., & Finn, O. J. (Under review). Recovery of tumor antigen (MUC1) specific antibody following successful stress reduction in breast cancer patients randomized to a psychological intervention in addition to standard therapy.

Andersen, B.L., Kiecolt-Glaser, J.K., & Glaser, R. (1994). A biobehavioral model of cancer stress and disease course. *American Psychologist, 49,* 389-404.

Cyranowski, J.C., Aarestad, S.L., & Andersen, B.L. (1999). The role of sexual self schemas in a diathesis-stress model of sexual dysfunction. *Applied and Preventive Psychology, 8 (3),* 217-228.

Golden-Kreutz, D.M., Courtney, M.E., & Andersen, B.L. (Under review). Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment.

Yurek, D., Farrar, W., & Andersen, B.L. (Accepted pending revisions). Breast cancer surgery: Comparing surgical groups and determining individual differences in post operative sexuality and body change stress. *Journal of Consulting and Clinical Psychology.*

REPORTS

Stress and Immune Responses After Surgical Treatment for Regional Breast Cancer

*Barbara L. Andersen, William B. Farrar, Deanna Golden-Kreutz, Leigh Ann Kutz, Robert MacCallum, Mary Elizabeth Courtney, Ronald Glaser**

Background: **Adults who undergo chronic stress, such as the diagnosis and surgical treatment of breast cancer, often experience adjustment difficulties and important biologic effects. This stress can affect the immune system, possibly reducing the ability of individuals with cancer to resist disease progression and metastatic spread. We examined whether stress influences cellular immune responses in patients following breast cancer diagnosis and surgery.** ***Methods:*** **We studied 116 patients recently treated surgically for invasive breast cancer. Before beginning their adjuvant therapy, all subjects completed a validated questionnaire assessing the stress of being cancer patients. A 60-mL blood sample taken from each patient was subjected to a panel of natural killer (NK) cell and T-lymphocyte assays. We then developed multiple regression models to test the contribution of psychologic stress in predicting immune function. All regression equations controlled for variables that might exert short- or long-term effects on these responses, and we also ruled out other potentially confounding variables.** ***Results:*** **We found, reproducibly between and within assays, the following: 1) Stress level significantly predicted lower NK cell lysis, 2) stress level significantly predicted diminished response of NK cells to recombinant interferon gamma, and 3) stress level significantly predicted decreased proliferative response of peripheral blood lymphocytes to plant lectins and to a monoclonal antibody directed against the T-cell receptor.** ***Conclusions:*** **The data show that the physiologic effects of stress inhibit cellular immune responses that are relevant to cancer prognosis, including NK cell toxicity and T-cell responses. Additional, longitudinal studies are needed to determine the duration of these effects, their health consequences, and their biologic and/or behavioral mechanisms. [J Natl Cancer Inst 1998; 90:30–6]**

A diagnosis of cancer and cancer treatments are objective, negative events in an individual's life. Although negative events do not always produce stress and a lowered quality of life, data from many studies document severe, acute stress at cancer diagnosis *(1)* and during recovery *(2)*. The negative psychologic responses of individuals with cancer to the diagnosis and treatment are important in their own right because these responses are targets for cancer control efforts *(3,4)*. In addition, data suggest that stress responses are accompanied by nonrandom (i.e., correlated) negative changes in a broad range of immune responses. This study examines from a biobehavioral perspective whether stress influences cellular immunity in women with breast cancer after diagnosis of breast cancer and during the postsurgical period *(5)*.

Meta-analyses *(6,7)* suggest that psychologic stress and the experience of life stressors are reliably associated with negative immune alterations in noncancer subjects; i.e., "higher" levels of stress (e.g., self-reports of stress or negative affects, such as sadness or clinical diagnoses of depression) are related quantitatively and functionally to "reduced" cellular immune responses, such as lowered natural killer (NK) cell lysis. This effect has been found regularly for individuals in the midst of chronic stressors, and some of the largest responses and changes have been found for lengthy stressors and those that have interpersonal components.

Illustrative data come from Kiecolt-Glaser, Glaser, and colleagues *(8–11)*, who have followed individuals during the long, stressful experience of giving care to a spouse diagnosed with Alzheimer's disease. Not surprisingly, caregivers report high levels of distress and negative affect as they cope with their relative's difficult behavior and mental deterioration *(8)*. Moreover, these researchers have found, for example, that NK cells obtained from caregivers are less responsive to the cytokine recombinant interferon gamma (rIFN γ) and recombinant interleukin 2 (rIL-2) than are cells obtained from matched community control subjects *(9)*. In addition, these highly stressed subjects have a poorer proliferative response to mitogens *(8)*, exhibit substantial deficits in the antibody and virus-specific T-cell responses to an influenza virus vaccine *(10)*, and demonstrate stress-related defects in wound repair *(11)*.

There are fewer data on the relationship between stress and immunity among cancer patients. Levy et al. *(12)* reported on these relationships in 66 women with stage I or II breast cancer 3 months after treatment (lumpectomy or mastectomy with or without adjuvant therapy). In ad-

**Affiliations of authors:* B. L. Andersen (Department of Psychology, Institute for Behavioral Medicine Research, and Comprehensive Cancer Center), W. B. Farrar (Department of Surgery, College of Medicine, and Comprehensive Cancer Center), D. Golden-Kreutz, M. E. Courtney (Department of Psychology), L. A. Kutz (Department of Medical Microbiology and Immunology, College of Medicine), R. MacCallum (Department of Psychology and Institute for Behavioral Medicine Research), R. Glaser (Department of Medical Microbiology and Immunology, Institute for Behavioral Medicine Research, College of Medicine, and Comprehensive Cancer Center), The Ohio State University, Columbus.

Correspondence to: Barbara L. Andersen, Ph.D., Department of Psychology, The Ohio State University, 1885 Neil Ave., Columbus, OH 43210-1222. E-mail: Andersen.1@osu.edu

See "Notes" following "References."

© Oxford University Press

dition to finding that estrogen receptor status predicted NK cell lysis, these researchers found that social support—a variable hypothesized to *reduce* stress—contributed significantly to a regression model predicting *higher* NK cell activity. These findings suggest that how a person responds to stress may also influence how stress, in turn, influences the immune response.

There is considerable evidence that patients with cancer express abnormal cellular immune responses; these abnormal responses have been found in patients with many different types of cancer *(13–15)*, including breast cancer *(16,17)*. Stressors are not generic, and they would not be expected to have identical physiologic outcomes. So too, the immune response involves a cascade of responses and events that can occur over time. For these reasons, we used a homogeneous breast cancer subject sample and timing of assessment to test the relationship between stress and several components of the cellular immune response, including NK cell and T-cell functions.

Women who had been diagnosed with breast cancer and who had undergone surgery for the breast cancer were studied before they began adjuvant therapy. Since we were interested in the contribution of stress in predicting an immune response above and beyond known correlates, we controlled for naturally occurring factors in our statistical analyses that affect the immune responses—specifically, age, disease stage (lymph node status), and recovery (days since surgery) *(18)*. Because the immune system contains a considerable amount of redundancy, we focused on three components that would each provide important, but complementary, information.

First, we measured NK cell lysis. We chose to measure NK cell lysis because those cells are believed to act early in the immune response and they have been demonstrated to play an important role in immune surveillance against tumors and virally infected cells *(19–21)*. Second, we measured the ability of the NK cells to respond to rIFN γ and rIL-2. It has been shown that lymphokine-activated killer (LAK) cells are highly cytotoxic against a wider variety of tumor cells than those lysed by resting NK cells *(22)*, an effect also observed in patients with breast cancer *(23)*. Finally, to obtain information on the T-cell response, we measured the response of peripheral blood leukocytes (PBLs) to two mitogens—phytohemagglutinin (PHA) and concanavalin A (Con A)—and we induced proliferation by stimulating the T cells with a monoclonal antibody (MAb) to the T-cell receptor.

Subjects and Methods

Patient Eligibility and Data Collection

Participants were 116 women who had been diagnosed with invasive breast cancer and who were surgically treated within the last 4 months but who had not yet begun adjuvant treatment. Women were from 14 to 101 days (mean = 37 days; median = 33 days) after surgery for stage II (70%) or III (30%) invasive breast cancer. We used the American Joint Committee on Cancer and the International Union Against Cancer staging system. The women ranged in age from 31 to 84 years (mean = 52 years). Recruited consecutively from mid-1994 to early 1997, the majority (82%) were being treated at a National Cancer Institute-designated, university-affiliated Comprehensive Cancer Center, and the remainder (18%) were receiving treatment at local community hospitals. All women came to the General Clinical Research Center at the university where psychologic, behavioral, and medical data were collected and a 60-mL blood sample was taken from them. Assessments were conducted between 8:00 AM and 12:00 AM to reduce diurnal variability.

Stress Measure

The Impact of Event Scale (IES) *(24)* is a standardized self-report questionnaire used to examine intrusive thoughts ("I had dreams about being a cancer patient," "Other things kept making me think about cancer") and avoidant thoughts and actions ("I tried not to talk about it," "I was aware that I still had a lot of feelings about cancer, but I didn't deal with them") concerning cancer. Fifteen items are used, and women rate each event or feeling in terms of the frequency of occurrence (i.e., "not at all," "rarely," "sometimes," and "often") during the previous 7 days. Scores range from 0 to 75. For this sample, descriptive statistics were as follows: range, 0–65; mean = 26; median = 25; and standard deviation = 15.2. The scale has satisfactory reliability with internal consistency of .78–.82 and a 2-week test–retest reliability of .79–.89, respectively. The validity of the measure is suggested by data indicating that individuals who experience involuntary, distress-related thoughts following traumatic life events are also those who suffer the greatest negative effects psychologically [e.g., *(2)*].

Immune Assays

Blood cell separation. PBLs were isolated from 60 mL of venous blood by use of Ficoll gradients (Pharmacia Biotech, Inc., Piscataway, NJ). The isolated leukocytes were then washed in calcium- and magnesium-free phosphate-buffered saline and counted on a Coulter counter (Coulter Corp., Miami, FL). Aliquots of 8×10^6 isolated PBLs were suspended again in 0.8 mL of RPMI-1640 medium supplemented with 10% fetal bovine serum, 0.75% sodium bicarbonate, 2 m*M* L-glutamine, and 10 μg/mL of ciprofloxacin.

Quantification of total T lymphocytes, T-cell subsets, and NK cells. Isolated PBLs were absorbed with MAbs conjugated to either fluorescein isothiocyanate or rhodamine according to the cell surface marker being studied: total T cells (CD3, fluorescein isothiocyanate), T4 subset (CD4, rhodamine), T8 subset (CD8, fluorescein isothiocyanate), and NK cells (CD56, rhodamine). All MAbs were purchased from Coulter Corp. Briefly, 0.5×10^6 cells were incubated with the MAb for 15 minutes at room temperature. After the incubation, the cells were fixed, and the red blood cells were lysed with Optilyse C, a buffered solution containing 1.5% formaldehyde, according to the manufacturer's instructions (Coulter Corp.). Samples were analyzed with the use of a Coulter EPICS Profile II flow cytometer as described previously *(8)*.

NK cell cytotoxicity. To determine NK cell activity, a microtiter ^{51}Cr-release cytotoxicity assay was used as described previously *(9,25)*. The target cells used were K-562 cells, an NK cell-sensitive human myeloid cell line. Target cells, labeled overnight for 16 hours with ^{51}Cr, were placed in triplicate wells of 96-well V-bottom plates, and PBLs were added, resulting in effector-to-target (E:T) cell ratios of 100:1, 50:1, 25:1, 12.5:1, and 6.25:1.

NK cell response to cytokines. Procedures for treatment of PBLs with rIFN γ and rIL-2 involved preparing isolated PBLs at a concentration of 3×10^6 cells/mL in complete RPMI-1640 medium and then seeding the cells into three replicate tissue culture tubes (Falcon, Becton Dickinson and Co., Lincoln Park, NJ) at 6×10^6 cells per tube. Cells were incubated in complete RPMI-1640 medium alone or complete medium supplemented with 250 IU/mL rINF γ or 60 IU/mL rIL-2 (Genzyme, Boston, MA). Cell suspensions were gently mixed and then incubated at 37 °C in an atmosphere of 5% CO_2 for 65 hours. For the assay, triplicate aliquots of cell suspensions were placed in wells of V-bottom plates, with E:T cell ratios of 50:1, 25:1, 12.5:1, 6.25:1, or 3.13:1. In addition, six wells with target cells and medium only and target cells with detergent (5% sodium dodecyl sulfate in phosphate-buffered saline) were prepared to determine spontaneously released chromium and maximal lysis, respectively. The plates were centrifuged at 300*g* for 5 minutes at 20 °C to bring the effector and target cells into close contact; they were then incubated at 37 °C in an atmosphere of 5% CO_2 for 5 hours. After this incubation, the plates were centrifuged at 300*g* for 5 minutes at 20 °C, 100 μL of supernatant was collected from each well, and counts per minute were determined by use of a Beckman 9000 gamma counter (Beckman Instruments, Inc., Fullerton, CA) as described previously *(9,26)*.

Blastogenic response to PHA, Con A, and MAb to the T3 receptor. The concentrations for PHA and Con A used were 2.5, 5.0, and 10.0 μg/mL. To measure the blastogenic response to the MAb to the T-cell receptor, we used the following three dilutions of the purified MAb: 32:1, 64:1, and 128:1. For all three assays isolated, PBLs seeded in triplicate at 0.5×10^5 per well were incubated for 68 hours at 37 °C in 96-well flat-bottomed plates and then labeled for 4 hours with MTS, i.e., 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt

Corp., Madison, WI) to measure proliferative response. Briefly, the MTS procedure is a radioactive calorimetric procedure that labels metabolically active cells via reduction of a colored substrate. The amount of proliferation was determined by optical density of the suspension in the well. Optical density determinations were performed by use of a Titertek Multiscan MCC microplate reader (Flow Laboratories, Inc., Finland) at a determination wavelength of 492 nm and a reference wavelength of 690 nm as has been noted *(27,28)*.

Statistical Analyses

Preliminary analyses. Before conducting the principal analyses, we checked the data for the contribution of "nuisance" variables (covariates) that could potentially be related to psychologic stress, immune outcomes, or both [*see (25)* for a discussion]. The variables examined were measures of aspirin, alcohol, caffeine, and nicotine intake; amount of sleep; plasma albumin level (as an indicator of nutritional status); incidence of recent infectious illness; and the Karnofsky performance status rating. We examined the relationships between these variables and each of the three sets of outcome variables: NK cell lysis, ability of NK cells to respond to rIFN γ and rIL-2, and the blastogenic response of PBLs to Con A, PHA, and the T3 MAb. Analysis of variance was used for the categorical independent variables, and simple correlations were used for numerically scaled independent variables.

Screening of these potential covariates involved examination of the relationships between 11 covariates and 20 dependent variables, or a total of 220 bivariate associations. Of these 220 associations, 15 were found to be statistically significant at .05 significance level. This number of significant effects is only slightly more than would be expected by chance alone (i.e., 220 × .05 = 11). Inspection of the significant relationships showed that many of them were attributable to the influence of a few outliers in the data. To be conservative, all of the regression analyses described below were run twice, once including and once excluding those covariates that had significant bivariate associations with the relevant dependent variables. In no case were results of the regression analyses significantly altered by the inclusion of the covariates. Given this fact and the consistently weak relationships of the covariates to the dependent variables, we do not report further results involving the covariates.

Principal analyses. The principal analyses assess the relationship between the IES measure of psychologic stress and the following three sets of outcome measures: 1) NK cell lysis at five E:T ratios, 2) response of NK cells to rIFN γ and rIL-2 stimulation at five E:T ratios each, and 3) the PBL blastogenic response to PHA and Con A and proliferative response to the T3 MAb at three concentrations or dilutions each.

We were interested in the role of stress in predicting these outcomes, over and above the impact of disease and recovery variables on the immune response. Thus, we chose to control for three variables: 1) age, which is associated with down-regulation of the immune system; 2) disease stage, which is an indicator of the extent or burden of disease; and 3) days since surgery, which is an indicator of the degree of recovery from surgical stress and related factors (e.g., anesthesia).

Using hierarchical multiple regression *(29)*, we tested the predictive value of psychologic stress for the measured immune outcomes. This procedure enters variables in a specified sequence and, at the final step, provides a test of the variance of the dependent variable (immune outcome) due to the predictor (stress), above and beyond the contribution of the control variables (age, stage, and days since surgery). In these regression analyses, age, days since surgery, and IES were considered as numerical variables. Stage was a categorical variable with two levels: II versus III.

For all of the analyses described below, any missing data were managed by the pairwise deletion technique, wherein each bivariate association is estimated with the use of all subjects for whom measures on both variables are available. This approach allows for more complete usage of available data than do alternative procedures (e.g., listwise deletion). For all of the dependent variables except the response of NK cells to rIFN γ, the quantity of missing data was small—with never more than 10 observations missing for any bivariate association. Effective sample sizes for the regression analyses ranged from 113 for the NK cell lysis ratios to 103 for T3 MAb values. For rIFN γ measures, sample sizes varied from 85 to 49 across the range of concentrations employed.

For each analysis, we provided three regression models: models A, B, and C. Model A includes only the control (independent) variables (i.e., age, stage, and days since surgery) in predicting the immune outcome (e.g., NK cell lysis). Predictors in model A were introduced simultaneously because we had no basis for or a strong interest in investigating their effects in any particular sequence. Model B includes the three control variables as well as the psychologic stress variable (IES) in the prediction of the immune outcome. Of particular interest in this analysis was the increment in the squared multiple correlation (R^2) from model A to model B (i.e., R^2_{B-A}), indicating variance in a dependent variable (e.g., NK cell lysis) attributable to stress (IES) beyond that explained by the control predictors. In addition, the standardized regression beta (β) for the psychologic stress variable (IES) in model B (i.e., β_{Stress}) indicates the magnitude and direction of the influence of this predictor on the dependent variable. The significance of the β weight was also tested. Finally, model C indicates the contribution of psychologic stress as the lone predictor; this third model provides the simple association between psychologic stress and immune function.

Results

Analyses Predicting NK Cell Lysis

Table 1 provides the results from the three models, A, B, and C, predicting NK cell lysis. For model A, in which age, stage, and days since surgery are the independent variables, R^2_A was small and nonsignificant for every E:T ratio (all F ratios were <1.0). Because the percentage of NK cells available would influence the

Table 1. Results of regression analyses for predicting natural killer (NK) cell lysis across six effector-to-target cell (E:T) ratios

	Dependent variable: NK cell lysis at E:T ratios					
	100:1	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.005	.007	.012	.015	.020	.023
Model AA, R^2_{AA}†	.085	.148	.185	.233	.250	.241
Model B‡						
R^2_B	.135	.212	.238	.268	.275	.253
R^2_{B-AA}§	.050	.064	.053	.035	.025	.012
β_{Stress}‖	−.234	−.265	−.240	−.194	−.165	−.115
$t(df = 110)$¶	−2.462	−2.921	−2.672	−2.223	−1.892	−1.280
P	.016	.004	.008	.028	.062	.204
Model C#						
R^2_C	.067	.091	.084	.066	.056	.032
$t(df = 110)$¶	−2.826	−3.338	−3.199	−2.811	−2.558	−1.867
P	.006	.002	.002	.006	.012	.066

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell lysis. The R^2_A is the total variance in NK cell lysis explained by these three predictors.

†Model AA includes model A variables plus the control predictor percentage of NK cells for the immune outcome, NK cell lysis. The R^2_{AA} is the total variance in NK cell lysis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell lysis. The R^2_B is the total variance in NK cell lysis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell lysis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, NK cell lysis. The R^2_C is the total variance in NK cell lysis explained by stress; this model provides the simple association between psychologic stress and immune function.

total NK cell activity as measured by lysis, we next added the percentage of NK cells, as determined by flow cytometry, into the analyses as an additional, independent control variable as shown (model AA). Across all E:T ratios, the R^2_{AA} values suggested that this variable added significant variance, as predicted, yielding R^2_{AA} values ranging from .085 to .250.

More important was the addition of the stress variable (IES) as a predictor, shown in model B. The value of R^2_B for lysis was noticeably larger than that of R^2_{AA}, and it provided a significant increment in prediction across the E:T ratios. These data indicate that the measure of psychologic stress that was used accounted for significant variance in NK cell lysis above and beyond that explained by age, stage, days since surgery, and percentage of NK cells. Moreover, the sign of the β regression coefficient for IES was negative, as predicted, indicating that an increase in measured stress was associated with a decline in NK cell lysis. The *t* tests for these coefficients were significant at five of the six E:T ratios. Also, no other predictor in model B had a significant regression coefficient.

We also provide the regression results when only IES was used as a predictor, eliminating the control predictors from the model (model C in Table 1). These results showed that the simple association between IES and NK cell lysis was statistically significant at five of the six E:T ratios.

Table 2. Results of regression analyses for predicting natural killer (NK) cell response to recombinant interferon gamma (rIFN γ) across five effector-to-target cell (E:T) ratios

	Dependent variable: NK cell response to rIFN γ at E:T ratios				
	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.025	.097	.080	.138	.124
Model B†					
R^2_B	.041	.151	.197	.257	.208
R^2_{B-A}‡	.016	.054	.117	.119	.084
β_{Stress}§	−.128	−.244	−.358	−.358	−.301
t	−1.104	−2.190	−3.203	−3.084	−2.083
df‖	82	81	74	65	46
P	.274	.032	.002	.004	.044
Model C¶					
R^2_C	.015	.077	.149	.149	.088
t	−1.128	−2.586	−3.581	−3.343	−2.080
df‖	82	81	74	65	46
P	.264	.012	.002	.002	.044

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell response. The R^2_A is the total variance in NK cell response explained by these three predictors.

†Model B includes model A control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell response. The R^2_B is the total variance in NK cell response explained by the three control predictors and the stress predictor.

‡R^2_{B-A} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell response.

§β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

‖*df* refers to the degrees of freedom in model B.

¶Model C includes stress as the only predictor of the immune outcome. NK cell response. The R^2_C is the total variance in NK cell response explained by stress; this model provides the simple association between psychologic stress and immune function.

Analyses Predicting Response of NK Cells to Cytokines

Results for the NK cell response to rIFN γ are provided in Table 2 and show a similar pattern. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A was small to moderate, ranging from .025 to .138. When stress (IES) was added to the model B regression, the R^2 values were statistically significant at all but one E:T ratio (50:1). Furthermore, the increments in the prediction due to IES, R^2_{B-A}, were significant and ranged from .054 to .119. This value reflects the proportion of variance in the cell response accounted for by stress (IES) beyond that explained by the control variables. Again, the negative weight of β for IES in model B indicated a negative influence of psychologic stress on the response of the NK cells to rIFN γ. Again, no other predictor in model B had a significant regression coefficient. Finally, the results for model C in Table 2 showed a simple association between IES and the rIFN γ response. These correlations were significant at four of the five E:T ratios; the proportions of variance accounted for were in the range of .077 to .149.

We attempted to calculate a parallel set of regressions for the response of NK cells to rIL-2. However, cells from a large proportion of the patients (62%) had no response to rIL-2. When the regressions were conducted on data obtained from the remaining patients (38%), the addition of stress (IES) in model B produced a significant R^2 value at the 25:1 E:T ratio only. It appeared that the majority of the subjects' NK cells did not respond to treatment with rIL-2.

Analyses Predicting Blastogenic Response of PBLs to Con A, PHA, and the T3 MAb

Table 3 shows regression results for the Con A and PHA blastogenic responses across three concentrations each. Because the findings are similar for both assays, they will be discussed together. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A for Con A ranged from .035 to .054 and was of similar magnitude for PHA, ranging from .022 to .033. Since the number of total T cells available will affect the blastogenesis values, we next added the number of T3-positive cells into the analyses as an additional, independent control variable as shown by the step model AA. Across all concentrations for each mitogen, the value of R^2_{AA} suggested that this variable added variance, yielding the R^2_{AA} values ranging from .105 to .125 for Con A and from .023 to .033 for PHA.

The addition of stress (IES) to the regression for blastogenesis added significant variance, as indicated in model B. All of the R^2 values were statistically significant. Considering the increments in R^2 due to stress (IES), these were significant and ranged from .032 to .061 for Con A and from .047 to .060 for PHA, reflecting the proportion of variance in the blastogenesis accounted for by IES beyond that explained by the control variables. Again, the negative β weights for IES in model B indicated a negative influence of psychologic stress on the blastogenic responses

sults of regression analyses for predicting the blastogenic response to concanavalin A (Con A) and phytohemagglutinin A (PHA) across three concentrations each

	Dependent variable: blastogenic response of mitogen					
	Con A			PHA		
	10 μg/mL	5 μg/mL	2.5 μg/mL	10 μg/mL	5 μg/mL	2.5 μg/mL
Model A. R^2_A*	.035	.043	.054	.022	.024	.033
Model AA. R^2_{AA}†	.105	.125	.115	.023	.024	.033
Model B‡						
R^2_B	.166	.174	.147	.083	.074	.080
R^2_{B-AA}§	.061	.049	.032	.060	.050	.047
β_{Stress}‖	−.255	−.229	−.187	−.256	−.234	−.229
$t(df = 103)$¶	−2.668	−2.401	−1.927	−2.521	−2.299	−2.254
P	.010	.018	.058	.014	.024	.026
Model C#						
R^2_C	.053	.065	.053	.070	.054	.052
$t(df = 108)$¶	−2.443	−2.724	−2.443	−2.857	−2.489	−2.441
P	.016	.008	.016	.006	.014	.016

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, blastogenesis. The R^2_A is the total variance in blastogenesis explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, blastogenesis. The R^2_{AA} is the total variance in blastogenesis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, blastogenesis. The R^2_B is the total variance in blastogenesis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the blastogenesis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, blastogenesis. The R^2_C is the total variance in blastogenesis explained by stress; this model provides the simple association between psychologic stress and immune function.

across concentrations. Moreover, no other predictor in model B had a significant regression coefficient. Finally, results for model C in Table 3 showed a simple association between stress (IES) and the blastogenic response. These correlations were significant for each concentration of Con A and PHA.

Table 4 shows regression results for the proliferative response of T cells to three different dilutions of the T3 MAb. For model A, the control R^2 values were not significant for any dilution. Addition of number of T3-positive cells available as a control increased the variance accounted for as shown by the step model AA. The R^2_{AA} values ranged from .088 to .143. However, increments in R^2 due to the addition of stress (IES), as shown by R^2_{B-AA}, were significant, ranging from .056 to .067. This indicates that about 6% of the variance was accounted for by stress (IES) beyond that explained by the control variables. Once again, no other predictor in model B had a significant regression coefficient. Results for model C again showed the simple, significant association of stress (IES) with the response to the T3 MAb at all dilutions, with R^2_c values of .092 to .102.

Discussion

Any immune response involves a complex cascade of events that occur over time. Studies suggest that the peripheral products of stress can play numerous roles in regulating immunity, and so the effects of stress will, necessarily, be variable. Current research suggests, for example, that the acute stressors, both real stressors [e.g., parachute jumps *(30)*] and artificial stressors [e.g., experimental tasks including speech or math stress *(31)*], are correlated with the mobilization (increase) of NK cells. These changes are thought to be a result of alterations in cell trafficking. In contrast, studies of chronic stressors [e.g., bereavement, caregiving, or divorce *(7,9)*] suggest that stress can have an effect on the ability of NK cells to lyse a target cell, the ability of NK cells to respond to rIFN γ and rIL-2 *in vitro*, and other aspects of the cellular immune response.

Our results suggest that stress, as assessed via a self-report measure of intrusive and avoidant thoughts and behaviors about cancer, was related to a negative effect on NK cell lysis, the ability of NK cells to respond to two cytokines, the blastogenic response of PBLs to two mitogens, and the proliferative response to MAb T-cell receptor. These effects were inhibitory and of similar magnitude (i.e., reliable), both between the assays and within an assay (i.e., across E:T ratios and mitogen concentrations). The analyses controlled for variables that might also be expected to exert short-term or long-term effects on immunity—such as age, stage of disease, and days since surgery—and ruled out other potentially confounding variables (e.g., nutritional status) that might also be influential. These controls reduced the plausibility of alternative, rival hypotheses for these consistent findings.

It is recognized that NK cells mediate natural immunity, but some researchers *(32)* suggest that their role in health generally has been underestimated. For example, there is evidence to suggest that the NK cells participate either directly or indirectly in multiple developmental, regulatory, and communication networks of the immune system. Furthermore, NK cells are efficient effector cells that not only are equipped for cell killing, but also are capable of rapid responses to exogenous or endogenous signals by producing cytokines and other factors involved in interactions between immune and nonimmune cells *(20)*.

The ability to spontaneously lyse a broad range of infected cells or tumor cells is the best known functional attribute of NK cells *(20,22)*. Consistent with previous reports, these data suggest that stress may impair this important process. Our findings highlight the specific effect of cancer stress on immune function, whereas prior data obtained by Levy et al. *(33)* had suggested that women's reports of fatigue were related to lower levels of NK cell lysis. Chronically low levels of NK cell activity occur in patients with cancer, particularly when there are large tumor burdens or disseminated metastases *(32)*. In general, patients with low NK cell activity appear to be at higher risk for infections, to have more prolonged diseases, or to suffer more severe symptoms

Table 4. Results of regression analyses for predicting proliferative response of peripheral blood leukocytes to a monoclonal antibody to T-cell receptor (T3) across three dilutions

	Dependent variable: proliferative response at dilutions		
	128:1	64:1	32:1
Model A, R^2_A*	.026	.052	.064
Model AA, R^2_{AA}†	.088	.104	.143
Model B‡			
R^2_B	.155	.160	.200
R^2_{B-AA}§	.067	.056	.057
β_{Stress}‖	−.273	−.249	−.252
$t(df = 101)$¶	−2.747	−2.514	−2.604
P	.008	.014	.012
Model C#			
R^2_C	.102	.092	.094
$t(df = 101)$¶	−3.452	−3.255	−3.307
P	.002	.002	.002

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, proliferative response. The R^2_A is the total variance in proliferation explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, proliferation. The R^2_{AA} is the total variance in proliferation explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, proliferation. The R^2_B is the total variance in proliferation explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the proliferation outcome.

‖β_{Stress} is the standardized beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶*df* refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, proliferation. The R^2_C is the total variance in proliferation explained by stress; this model provides the simple association between psychologic stress and immune function.

than patients whose NK cell activity remains normal *(32,34)*.

A variety of biologic response modifiers are known to increase the activation, proliferation, or cytotoxicity of NK cells *(20)*. Among the best known activators of NK cells are IL-2 and IFN γ. Our data show that the physiologic changes associated with psychologic stress inhibited NK cell lysis. Stress also affected the ability of NK cells to respond to rIFN γ, a finding that is consistent with two previous reports involving another life stressor [i.e., caregiving for a spouse with Alzheimer's disease *(9,26)*]. It is interesting that NK cells from 62% of the women did not respond to rIL-2. In subsequent analyses comparing women who did have an rIL-2 response with those who did not, no stress or disease variable differentiated the two groups. Further studies will need to be performed to explore this result, although it is possible that the lack of responsiveness of NK cells to rIL-2 may be due to an overproduction of prostaglandin E_2 by monocytes. It has been suggested that in breast cancer patients prostaglandin E_2 decreases IL-2 production in effector cell populations, resulting in the down-regulation of the expression of the IL-2 receptor on NK cells *(23)*. Follow-up studies will need to pursue and clarify this difference in cytokine responses.

It has been shown that the ability of PBLs to respond to PHA is reduced, in general, in cancer patients *(35)*; this lowered response is related to tumor burden and declines in the ability of PBLs to respond to PHA with disease progression *(36)*. The negative effect of stress on blastogenesis was replicated in this study across two mitogens, PHA and Con A, as well as in the response of T cells to an MAb against the T-cell receptor. These findings are consistent with correlational and experimental studies indicating that stress impairs the blastogenic response of PBLs to mitogens and virus-specific T-cell responses *(8,10,37–39)*. Mitogen-induced proliferation has been used to indicate the immune system's ability to respond to antigens from pathogens. Chronically stressed, but healthy, individuals showing decrements in the cellular immune response (including NK cell lysis and the response of the PBLs to mitogens) subsequently reported a higher incidence of infectious illnesses *(8)*. If this effect is reliable, these data would suggest that cancer patients who experience high levels of stress, lowered levels of responsive T lymphocytes, and decreased NK cell function may be at greater risk for infectious illnesses as they begin adjuvant therapy.

It is interesting that evidence is accumulating to suggest that psychologic and/or behavioral stress reduction interventions may *enhance* certain aspects of the cellular immune response, including NK cell lysis. In an early investigation, Kiecolt-Glaser et al. *(40)* studied 61 healthy adults living in a retirement home. After receiving 1 month of training in progressive muscle relaxation, the subjects showed evidence of a 30% increase in NK cell lysis in comparison with those who received no treatment or only social contact. Fawzy et al. *(41)* studied 61 patients with melanoma and reported that, 6 months after treatment, subjects receiving intervention had significantly higher levels of IFN alfa-augmented NK cell activity than those who received no treatment. These data suggest that, if behavioral interventions can reduce stress and enhance the cellular immune response, then health outcomes might improve.

In conclusion, these data show a down-regulation of different aspects of the cellular immune response associated with the psychologic stress that accompanies the diagnosis and initial surgical treatment of cancer. We note that these study participants are part of a larger effort testing the biobehavioral aspects of stress, immunity, and disease course *(5)*. It will be important to document the longitudinal nature of these findings, and future studies will provide such data. Moreover, half of the women who participated have been randomly assigned to receive a psychologic/behavioral intervention specifically designed to reduce stress, enhance quality of life, and test for the biologic mechanism—such as immune responses—that may mediate any positive effects of stress reduction on health and disease outcomes.

References

(1) Andersen BL, Anderson B, deProsse C. Controlled prospective longitudinal study of women with cancer: II. Psychological outcomes. J Consult Clin Psychol 1989;57:692–7.

(2) Moyer A, Salovey P. Psychosocial sequelae of

er and its treatment. Ann Behav
,18:110–25.
en BL. Surviving cancer. Cancer
4(4 Suppl):1484–95.
ia DE (Chair). Proceedings: Secretary's
ference to Establish a National Action Plan
Breast Cancer, Dec 14–15, 1993. Bethesda
,MD): National Institutes of Health, 1993.
Andersen BL, Kiecolt-Glaser JK, Glaser R. A biobehavioral model of cancer stress and disease course. Am Psychol 1994;49:389–404.
(6) Herbert TB, Cohen S. Depression and immunity: a meta-analytic review. Psychol Bull 1993;113:472–86.
(7) Herbert TB, Cohen S. Stress and immunity in humans: a meta-analytic review. Psychosom Med 1993;55:364–79.
(8) Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. Psychosom Med 1991;53: 345–62.
(9) Esterling BA, Kiecolt-Glaser JK, Bodnar JC, Glaser R. Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokines in older adults. Health Psychol 1994;13:291–8.
(10) Kiecolt-Glaser J., Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci U S A 1996;93:3043–7.
(11) Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet 1995;346:1194–6.
(12) Levy SM, Herberman RB, Lee J, Whiteside T, Kirkwood J, McFeeley S. Estrogen receptor concentration and social factors as predictors of natural killer cell activity in early-stage breast cancer patients. Confirmation of a model. Nat Immun Cell Growth Regul 1990; 9:313–24.
(13) Fortner JG, Kim DK, Hopkins L, Barrett MK, Pinsky CM, Day NK. Immunologic function in patients with carcinoma of the pancreas. Surg Gynecol Obstet 1980;150:215–8.
(14) Monson JR, Ramsden C, Guillou PJ. Decreased interleukin-2 production in patients with gastrointestinal cancer. Br J Surg 1986; 83:483–6.
(15) Feo Figarella E, Morillo F, Blanca I, Bianco NE. Failure of cell-mediated effector mechanisms in lung cancer. J Natl Cancer Inst 1984; 73:1–6.
(16) Anastasopoulos E, Reclos GJ, Baxevanis CN, Tsilivakos V, Panagiotopoulos N, Fotiou S, et al. Monocyte disorders associated with T cell defects in cancer patients with solid tumors. Anticancer Res 1992;12:489–94.
(17) Steinhauer EH, Doyle AT, Reed J, Kadish AS. Defective natural cytotoxicity in patients with cancer: normal number of effector cells but decreased recycling capacity in patients with advanced disease. J Immunol 1982;129:2255–9.
(18) Jubert AV, Lee ET, Hersh EM, McBride CM. Effects of surgery, anesthesia and intraoperative blood loss on immunocompetence. J Surg Res 1973;15:399–403.
(19) Herberman RB, Ortaldo JR. Natural killer cells: their roles in defenses against disease. Science 1981;241:24–30.
(20) Trinchieri G. Biology of natural killer cells. Adv Immunol 1989;47:187–376.
(21) Hersey P, Edwards A, Honeyman M, McCarthy WH. Low natural-killer-cell activity in familial melanoma patients and their relatives. Br J Cancer 1979;40:113–22.
(22) Whiteside TL, Herberman RB. Characteristics of natural killer cells and lymphocyte-activated killer cells. Immunol Allerg Clin North Am 1990;10:663–704.
(23) Baxevanis CN, Reclos GJ, Gritzapis AD, Dedousis GV, Missitzis I, Papamichail M. Elevated prostaglandin E_2 production by monocytes is responsible for the depressed levels of natural killer and lymphokine-activated killer cell function in patients with breast cancer. Cancer 1993;72:491–501.
(24) Horowitz M, Wilner N, William A. Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979;41:209–18.
(25) Kiecolt-Glaser JK, Glaser R. Methodological issues in behavioral immunology research with humans. Brain Behav Immun 1988;2:67–78.
(26) Esterling BA, Kiecolt-Glaser JK, Glaser R. Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. Psychosom Med 1996;58:264–72.
(27) Gieni RS, Li Y, Hay Glass KT. Comparison of [^{3}H]thymidine incorporation with MTT- and MTS-based bioassays for human and murine IL-2 and IL-4 analysis. Tetrazolium assays provide markedly enhanced sensitivity. J Immunol Methods 1995;187:85–93.
(28) Shobitz B. Steroids and central regulation of immune response. Meth Neuro Sci 1994;22: 510–52.
(29) Cohen J, Cohen P. Applied multiple regression/correlation analysis for the behavioral sciences. Hillsdale (NJ): Erlbaum, 1983.
(30) Schedlowski M, Jacobs R, Stratmann G, Richter S, Hadicke A, Tewes U, et al. Changes in natural killer cells during acute psychological stress. J Clin Immunol 1993;13:119–26.
(31) Uchino BN, Cacioppo JT, Malarkey W, Glaser R. Individual differences in cardiac sympathetic control predict endocrine and immune responses to acute psychological stress. J Pers Soc Psychol 1995;69:736–43.
(32) Whiteside TL, Herberman RB. Role of human natural killer cells in health and disease. Clin Diagn Lab Immunol 1994;1:125–33.
(33) Levy SM, Herberman RB, Maluish AM, Schlien B, Lippman M. Prognostic risk assessment in primary breast cancer by behavioral and immunological parameters. Health Psychol 1985;4:99–113.
(34) Cannon GB, Dean JH, Herbermann RB, Perlin E, Reid J, Miller C, et al. Association of depressed postoperative lymphoproliferative responses to alloantigens with poor prognosis in patients with stage I lung cancer. Int J Cancer 1980;25:9–17.
(35) Han T, Takita H. Depression of T lymphocyte response by non-T suppressor cells in lung cancer patients: a possible prognostic value of suppressor cell activity. Cancer 1979;44:2090–8.
(36) Ludwig CU, Hartmann D, Landmann R, Wesp M, Rosenfelder G, Stucki D, et al. Unaltered immunocompetence in patients with nondisseminated breast cancer at the time of diagnosis. Cancer 1985;55:1673–8.
(37) Baron RS, Cutrona CE, Hicklin D, Russell DW, Lubaroff DM. Social support and immune function among spouses of cancer patients. J Pers Soc Psychol 1990;59:344–52.
(38) Bartrop RW, Luckhurst E, Lazarus L, Kiloh LG, Penny R. Depressed lymphocyte function after bereavement. Lancet 1977;1:834–6.
(39) Locke SE, Kraus L, Leserman J, Hurst MW, Heisel JS, Williams RM. Life change stress, psychiatric symptoms, and natural killer cell activity. Psychosom Med 1984;46:441–53.
(40) Kiecolt-Glaser JK, Glaser R, Williger D, Stout J, Messick G, Sheppard S, et al. Psychosocial enhancement of immunocompetence in a geriatric population. Health Psychol 1985;4: 25–41.
(41) Fawzy FI, Kemeny ME, Fawzy NW, Elashoff R, Morton D, Cousins N, et al. A structured psychiatric intervention for cancer patients. II. Changes over time in immunological measures. Arch Gen Psychiatry 1990;47:729–35.

Notes

Supported by grants from the American Cancer Society (PBR-89); the Longaberger Company-American Cancer Society Grant for Breast Cancer Research (PBR-89A); the U.S. Army Medical Research Acquisition Activity grants (DAMD17–94-J-4165 and DAMD17–96–1–6294); Public Health Service grants R01MH51487 (National Institute of Mental Health), M01RR0034 (National Center for Research Resources), and CA16058 (National Cancer Institute), National Institutes of Health, Department of Health and Human Services; and the Department of Psychology and the College of Social and Behavioral Sciences at The Ohio State University.

We thank the participants for their assistance. In addition, we thank the following individuals for their contributions: Nicole Chaput, Angela Collier, Katheryn Pingel, Elizabeth Street, Jessica Walker, JoAnne Lester, and Beth Putz for accrual and conducting the psychologic and medical assessments; Annette Gilsey, Andrew Jackson, Bryan Laskowski, Marilyn Welt, and Susan Yep for assistance with the immune assays; and Jerry Tobler for support and comments on the manuscript.

Manuscript received May 12, 1997; revised September 25, 1997; accepted October 22, 1997.

Barbara Andersen, Ph.D., and colleagues at Ohio State University, Columbus, report that baseline measures of stress, specific to the diagnosis of cancer, were linked to levels of natural killer cell activity, T-cell responses, and other cellular responses "relevant to cancer prognosis."

It's still a big step from this finding to the question that Andersen would most like to answer: Can a stress reduction intervention influence cancer progression? But her larger study, plus two others now in progress in the United States and Canada, may help provide that answer over the next 6 years.

Andersen's larger study at Ohio State will involve 235 women with stage II or III breast cancer who are randomized, after surgery and before adjuvant therapy, into two groups, one of which will attend support groups for a year. The group sessions empasize both emotional support and education on, for instance, coping strategies.

All participants are assessed, first at enrollment and then 5 years following randomization to determine stress levels, cellular immune responses, and cancer recurrence. As of Dec. 1, 1997, 160 patients had been accrued. Recruitment should be completed in 1998, Andersen said, and results could be available in about 6 years.

While the step from reducing stress to reducing recurrence rates seems a giant one, the hypothesis has some evidence to back it. In the late 1980s, David Spiegel, M.D., a psychiatrist at Stanford University, discovered that breast cancer patients who received psychosocial support had better survival rates than patients in a control group who received no formal intervention.

Spiegel said he and his colleagues had set out to study the impact of a particular form of support on quality of life. They had not intended to look at survival. But after 10 years, they found that the 50 women in the support group (designed to encourage full "emotional expressiveness" about the cancer and allow patients to confront their feelings about the disease) had survival rates nearly twice those of the 36 patients in the control group. Mean survival for the intervention group was 36.6 months from the time of randomization compared with 18.9 months for the control group.

A few other small studies have had contradictory results. Most frequently cited is a randomized controlled trial at the University of California, Los Angeles, where Fawzy I. Fawzy, M.D., found that a psychosocial intervention was associated with longer survival in melanoma patients.

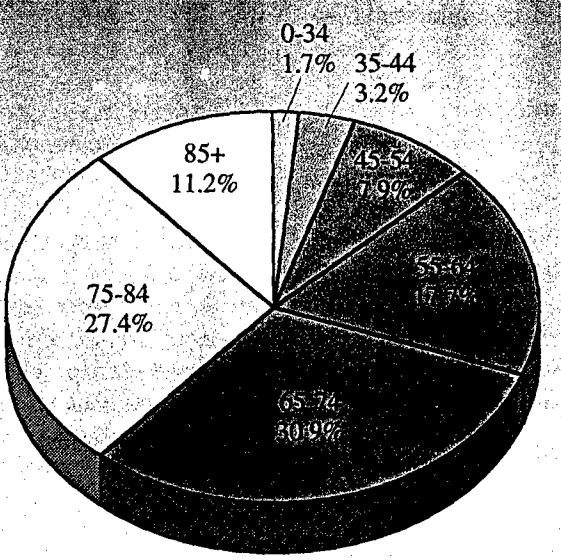
The other U.S. trial looking at stress reduction, immune factors, and cancer

Stat Bite

Age Distribution of Cancer Deaths in the United States

While cancer mortality has begun to decline in the United States, it is estimated that about 560,000 Americans died of the disease in 1997. Because cancer more often occurs in older age groups, more than two-thirds of cancer deaths occur after age 64.

Percent of cancer deaths by age group, all sites, 1990-1994



Source: *SEER Cancer Statistics Review, 1973-1994*/National Center for Health Statistics public use tapes.

tate cancer screening. Arnauld Villers, M.D., Ph.D., a urologist from the Hospital Purpan in Toulouse, France, said he expects the agency to allow general practitioners to recommend PSA testing for men 50 to 75 years of age within the next few months. Prostate cancer gained importance among the French public after former president Francois Mitterrand's diagnosis and subsequent death from the disease in 1996.

Participation rates in the screening trials vary partly due to randomization methods. Some of the trials randomize entire geographic populations. Then men in one area are offered screening. Acceptance of this offer is highest in Finland at 70%; Italy and Sweden are at 60%.

Other trials recruit men prior to randomization and seek to maximize participation so that men in the trial are more typical of the general population. With this approach, the Netherlands has 46% participation.

The study that is based in Antwerp, Belgium, managed to boost its participation rate from 18% to 34% by visiting the homes of men who are eligible to participate. Spain has reached only 23%, and that study's leaders don't expect participation to improve, due to the population's overall fear of detecting illness.

Strength from Diversity

Although the studies follow a core protocol (they must use PSA, employ one of two valid randomization approaches, ascertain prostate cancer mortality in both arms of the study, and apply quality control standards for application of the screening tests), they contain deliberate variations (J Natl Cancer Inst, June 21, 1995;87:868-871). They vary in the number of years between screenings, in the PSA measure that indicates the need for further testing, and in the screening tests provided along with PSA (they may or may not provide digital rectal exam or transrectal ultrasound.). Finally, the treatment options offered depend on each patient's urologist.

This lack of uniformity among the protocols is, technically speaking, an epidemiologists' nightmare. But Freda Alexander, Ph.D., of the University of Edinburgh, Scotland, chair of the ERSPC Epidemiology Committee, used an example to point out its added value. "We could just go with very frequent screenings to get the maximum effect, but that doesn't tell us how well much cheaper screening works." So some centers are using a 1-year screening interval, while others are waiting as long as 4 years between screenings.

Schröder agreed, "There will be a wealth of information coming from [the combined studies] concerning the optimization of the use of screening tests, the types of cancer detected at screening, and prognostic factor analysis that may allow greater selectivity of screening procedures in the future, with proper identification of the type of tumor that may benefit from early treatment."

To avoid contamination of the control group and because the study is looking for differences in mortality, study group members have committed to delay publishing endpoint data until 10-year followup is completed. But, Alexander added, "If evidence accrues that screening might influence shorter-term conditions, the ERSPC management committee could change that policy."

— Cori Vanchieri

Stress Reduction: Three Trials Test Its Impact on Breast Cancer Progression

Does psychological stress play a role in cancer progression and can reducing stress slow tumor growth? Some answers could be available soon after the year 2000 to this question, which has intrigued mental health specialists for several decades.

Up to now, the field of psychoneuroimmunology has yielded relatively little data related to cancer. In the area of infectious diseases, particularly colds, researchers have found a variety of links between psychological stress and the immune system. A few investigators have looked specifically at cancer patients and how the stress of diagnosis and treatment may affect immune response. Only a very few have ever designed an intervention to see whether stress reduction can improve immune function and slow cancer progression.

Dr. Barbara Andersen

Now, three such studies are under way, all randomized, controlled trials of support-group interventions with breast cancer patients. None of the trials has data on tumor recurrence or survival yet. But early findings from one of them, reported on page 30, support the hypothesis that cancer-related stress is associated with cellular immune responses that may play a role in tumor growth.

progression is under way at Stanford where Spiegel and colleagues are replicating the earlier study with a larger group. Initiated in 1990, the trial has 125 participants who were randomized into two groups, one of which attended support sessions.

Now about three-quarters of the way through a 10-year followup, the investigators are monitoring endocrine and cellular markers of immune function, such as cortisol levels and natural killer cell activity, as well as recurrence and survival rates. Spiegel said they expect to have some preliminary results published later this year, and final results, including survival data, could be ready around the year 2000.

A third trial on stress reduction and cancer progression is taking place in Canada at seven different sites. Led by Pamela Goodwin, M.D. at Mount Sinai Hospital, Toronto, the trial is replicating Speigel's intervention with 235 women. Goodwin said this study should have completed recruitment by the end of 1997 and that results, including survival data, could be available around 2000.

Controversy Continues

A major hypothesis in all three studies — that stress reduction can alter immune function in a way that influences cancer progression — is a controversial one, said Sheldon Cohen, Ph.D. and Bruce Rabin, M.D., University of Pittsburgh, in their editorial on page ___. There is too little known, for one thing, about the type and magnitude of the immune responses that influence cancer progression, they say.

Another problem in studying the role of psychosocial interventions are the number and complexity of factors that might independently influence immune responses and cancer progression. All three trials now in progress are controlling for known prognostic factors, such as the extent of lymph node involvement and whether the tumor cells had estrogen receptors. But numerous other factors could play a role, including the immunosuppressive effects of cancer treatment, the details of which are not completely known.

Another point noted by Cohen and Rabin — and one that turns up repeatedly in the literature on stress reduction and cancer survival — is that a support group could influence disease progression by means other than the stress reduction/immune response mechanism. For instance, supportive interventions might work because they encourage treatment compliance.

Spiegel said that he and colleagues examined this issue in their earlier study by reviewing participants' medical records. They found no difference in treatment that could account for the difference in survival rates. For that trial, "we've pretty much ruled out differences in treatment as an explanation," he said.

However, the impact of intervention on compliance with treatment is still an unknown. One hypothesis being tested in the Canadian study, said Goodwin, is that the psychosocial intervention improves survival by encouraging compliance. The Ohio State researchers are also looking at medical treatment, collecting data not only on prescribed treatment but also on the chemotherapy doses that each patient actually receives.

It is a key issue, Andersen said. "This is something we are looking at very closely."

— Caroline McNeil

To Build a Better Mousetrap, Use Human Parts

Historically disappointing results with mouse-based monoclonal antibodies (MAbs) have biased many clinicians against this approach to treating human diseases. Now, re-engineered antibodies are ready for a comeback, thanks to the persistence of a few researchers who were unwilling to abandon the idea.

One MAb, IDEC-C2B8 or rituximab, recently was approved by the Food and Drug Administration for treatment of a type of non-Hodgkin's lymphoma (see sidebar). Several others, such as HER2 for breast cancer and A33 and anti-EGP40 for colorectal cancer are in clinical trials. And at least two dozen other MAbs are in various stages of clinical testing in the cancer setting.

Such signs of progress have rekindled hope in those researchers who have continued over the past several decades to explore the basic MAb concept — that an antibody injected into a cancer patient could seek out a specific antigen on cancer cells, bind to that antigen, and activate the body's immune system to kill with great specificity only the cancer cells.

Dr. Thomas A.Waldmann

The breakthrough that turned that vision into clinical reality, according to Thomas A. Waldmann, M.D., chief of the metabolism branch at the National Cancer

Appendix B

- Unpublished Data -

Recovery of Tumor Antigen (MUC1) Specific Antibody Following Successful Stress Reduction in Breast Cancer Patients Randomized to a Psychological Intervention in Addition to Standard Therapy

Barbara L. Andersen[1], Deanna M. Golden-Kreutz[1], John McKolanis[2], William Malarkey[3], William B. Farrar[4], Mary DeLamatre[1], & Olivera J. Finn[2]

[1]Department of Psychology, 1885 Neil Avenue, The Ohio State University, Columbus, Ohio 43210-1222, USA

[2]Department of Molecular Genetics and Biochemistry, Univ. of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA

[3]Department of Internal Medicine, The Ohio State University School of Medicine, Columbus, Ohio 43210, USA

[4]Department of Surgery, The Ohio State University School of Medicine, Columbus, Ohio 43210, USA

Correspondence should be addressed to B.L.A.; e-mail andersen.1@osu.edu

ABSTRACT

Stress with breast cancer diagnosis and treatment negatively influences immune responses. We hypothesized that stress reduction might positively influence an anti-tumor immune response against a breast cancer antigen MUC1. Women surgically treated for regional breast cancer were randomized to psychological/behavioral intervention or assessment only study arms. Women receiving the intervention showed a significant lowering of stress as indexed by serum cortisol, fewer depressive symptoms, and prompt recovery and maintenance of anti-MUC1 antibody response. Assessment only women had higher cortisol, more depressive symptoms, and permanently lost anti-MUC1 antibody responses. These are the first experimental data showing a convergence of psychological, endocrine, and immune effects with a psychological/behavioral intervention, and, importantly, the intervention enhanced a breast cancer relevant immune response.

INTRODUCTION

A diagnosis of cancer and cancer treatments are objective, negative events in an individual's life. Although negative events do not always produce stress and a lowered quality of life, data from many studies document severe, acute stress at diagnosis[1] and the potential for continuing stress[2]. Stress and deterioration in quality of life are important targets for cancer control efforts[3,4] in that they co-occur with adverse biologic consequences.

The body's response to stress involves the autonomic, endocrine, and immune systems. Psychological stress is associated with the activation of the hypothalamic-pituitary-adrenal (HPA) axis, and cortisol, the main hormone to reflect adaptation to stress, is produced[5-7]. Psychological distress and stressors (i.e. negative life events) are also associated with immune system changes, primarily down-regulation[8,9].

In addition to each system being singly responsive to stress, the neuroendocrine and the immune systems provide an integrated mechanism necessary for maintenance of the body's proper defense function. For example, leukocytes are key effectors and provide an important representation of the state of activation for the immune system. Leukocytes can also make cytokines that, in turn, are available to regulate the production of hormones by the neuroendocrine system. Lymphocytes, on the other hand, have receptors for neuroendocrine peptides and hormones and have the ability to produce each as well. In sum, stress can produce perturbations in both the endocrine and the immune systems.

There is accumulating evidence that stress and its biologic consequences occur in the context of cancer. Our previous studies with women with breast cancer who were assessed during the post surgery recovery period found that high levels of stress were related to the down regulation of a panel of cellular immune responses, including NK cell function (i.e. lytic activity, response to rIFN-γ) and T cell function (i.e., proliferation and blastogenesis)[10]. Levy[11] also reported on stress and immunity in women with breast cancer and found that estrogen receptor status predicted NK cell lysis, and social support, a variable hypothesized to reduce stress, was correlated with higher NK cell activity. Together, these findings suggest that if an individual with

cancer is significantly stressed, and nothing is done to alleviate it, then stress may negatively influence his/her immune response.

Psychological intervention studies with cancer patients can produce impressive reductions in stress and improvements in quality of life. This is particularly true for breast cancer patients and patients at greatest risk for psychological/behavioral morbidity, such as those with more extensive disease[12]. However, few studies have measured endocrine and/or immune responses, instead relying on psychological or behavioral measures. An exception to this is a study by Fawzy et al.[13,14], who conducted a randomized investigation to reduce stress for newly diagnosed and surgically treated melanoma patients. They reported lower levels of mood disturbance and enhanced immune function (e.g. NK cell lysis) for the intervention group.

Psychological interventions designed for stressed but otherwise healthy individuals have yielded significant reductions in serum cortisol with concomitant improvements in the individuals' moods[15-19], yet unfortunately, immune measures were not included in these studies. Research focusing on the relationship between stress and immunity in humans has not included endocrine measures, and the immune measures were usually non specific (e.g. quantitative measures of cell number, functional measures of blastogenesis or lysis)[8,9], with few exceptions[20,21]. The study we report here used an experimental design that included psychological, endocrine, and immune measures, and, importantly, monitored a specific immune response against a breast tumor antigen, MUC1.

Patients with breast cancer develop humoral as well as cellular immune responses to several breast cancer related molecules, such as HER-2/neu, p53, and MUC1[22]. In general, the presence of an immune response against the tumor is correlated with a more favorable prognosis. Unlike the other antigens that are each expressed only in a subset of breast cancers, MUC1 is expressed by all breast cancers, primary tumors as well as metastases[23]. Varying but detectable levels of anti-MUC1 antibodies can be found in all patients. Furthermore, it has been shown that elevated levels of anti-MUC1 antibody and/or immune complexes present in patients' serum at the time of diagnosis strongly protect against disease progression and correlate with an increase in disease free

interval and overall survival[24]. Furthermore, the presence of a humoral response is suggestive of activation of other immune mechanisms, and so assessment of anti-MUC1 antibody served as a surrogate marker of an overall anti-tumor response in the patient. It has been shown, for example, that in addition to the humoral response, breast cancer patients generate weak but measurable cytotoxic T cell responses that have also been correlated with good prognosis[25,26].

Our intent was to experimentally determine if an intervention designed to reduce cancer related stress and enhance mood could also influence biologic responses, that is, to down regulate endocrine stress responses and up-regulate immune responses. Our biobehavioral model of cancer stress and disease course[27] suggests that enhanced biologic responses may accrue from stress reduction and improvements in quality of life resulting from psychological interventions. We selected women who had been diagnosed and surgically treated for regional breast cancer. Prior to beginning standard adjuvant therapy, all patients completed a questionnaire assessing symptoms of depression and provided a serum sample for assaying levels of cortisol and anti MUC1 antibody response. Women were randomized to one of two arms: Intervention and assessment or Assessment only. The 12 month psychological/behavioral intervention, designed to reduce stress and improve quality of life, consisted of an intensive phase with weekly sessions for 4 months and then a maintenance phase with monthly sessions for 8 months. Monitoring of all patients was repeated at 4, 8, and 12 months. Thus, the pretreatment assessment of anti-MUC-1 antibody and its recovery and maintenance post adjuvant cancer therapy provided a disease specific marker (and an overall marker of anti-tumor response) against which we assessed the immunologic consequence of a psychological/behavioral intervention. Additionally, the data provided the opportunity to examine psychological and endocrine mechanisms for an anti MUC1 antibody response.

RESULTS

Equivalence of study arms at pretreatment

Analyses were conducted to rule out the presence of pretreatment group differences on variables which could potentially be confounded with outcome, including sociodemographic

variables, aspects of disease/treatment, and health behavior correlates of stress. One way analysis of variance (ANOVA) comparisons (i.e. Group: Intervention vs. Assessment only) for the sociodemographic variables revealed no significant differences between groups on the variables of race, age, marital status, presence of a significant other (e.g. spouse), education, employment status, or annual personal income ($p > .05$).

Randomization also resulted in the groups being equivalent in important disease and treatment related variables. ANOVA's comparing groups revealed that the study arms were equivalent ($p's > .05$) on the variables of stage, tumor size, numbers of positive nodes, ER status, menopausal status, surgery type, incidence of radiation treatment, days since surgery, and Karnofsky Performance status at accrual. Perhaps even more important in view of the immune focus of the study, dose intensity was calculated for each of the chemotherapy drugs prescribed to each patient at the time of accrual. The agents were Cytoxan, Adriamycin, 5-FU, Methotrexate, and/or Taxol. ANOVA's indicated that the two study arms were recommended to receive equivalent doses of all chemotherapy drugs (adjusted for patient's body surface area), with the exception of the recommended dose for Adriamycin [$F(2, 73) = 5.80$, $p < .01$]. The Intervention group was recommended to receive a significantly higher dose ($M = 40.02$) of Adriamycin than the Assessment only group ($M = 35.17$). As this group difference in favor of the Assessment only arm went against the hypotheses for the study (i.e., we predicted that the Intervention group would have improved psychological, endocrine, and immune outcomes regardless of the magnitude of the standard therapy), the analyses did not control for this difference.

As the psychological outcome was depressive symptoms, we also tested for initial group differences on variables that are often correlated with acute stress or depressive symptoms, such as negative health behaviors (i.e. history of alcoholism/current alcohol use, current smoking), low rates of positive health behaviors (e.g. high fat/low fiber intake, low rates of exercise), or vegetative signs of depression (e.g. weight loss, sleep problems). One-way group comparison ANOVA's for these variables were not significant ($p's > .05$). Taken together, these preliminary analyses indicated that the randomization procedure was effective in establishing equivalence

between the study arms for sociodemographic, disease and treatment, and other variables which could covary with psychologic or biologic outcomes.

Effects of the intervention on stress reduction

A repeated-measures ANOVA was calculated to test the hypothesis that cortisol levels for women in the intervention group would decline following the intensive intervention, as compared to levels for women in the assessment only group. The Group x Time [$F(3, 73) = 3.02$, $p < .05$] interaction was significant, but the Group x Time x Stage interaction was not significant. More specifically, within-subjects contrasts indicated that mean cortisol levels in the Intervention group decreased significantly following the period of intensive intervention as compared to the cortisol levels for the Assessment only group. In fact, an examination of Figure 1 indicates that mean cortisol levels for Assessment-only women actually rose from the initial assessment to the four-month assessment, while Intervention group means declined during the same period.

A repeated-measures ANOVA was calculated to test the hypothesis that depressive symptoms (CES-D) would decrease for women in the Intervention arm following the intensive weekly intervention (i.e. from initial to 4 months), as compared the level of depressive symptoms for the patients randomized to Assessment only. Whereas there were no significant Group x Time interaction effects, the Group x Time x Stage interaction was significant [$F(3,83) = 2.79$, $p < .05$]. Within-subjects contrasts comparing the change in depressive symptoms from the initial assessment to the follow up assessments showed no significant differences. However, an examination of the CES-D means indicates that the depressive symptoms for Stage III women in the Intervention arm declined from the initial to the four month follow up, while the depressive symptoms for the Stage III patients in the Assessment only arm actually rose during the same period. There were no significant changes over time in CES-D means for Stage II patients.

Effects of the intervention on MUC1 specific antibody responses

For each of three serum dilutions, 1:20, 1:40, and 1:80, a repeated-measures ANOVA was calculated in order to test the hypothesis that anti MUC-1 antibody levels for women in the Intervention arm would recover following the intervention (i.e. 8 or 12 months), as compared to

levels for the women in the Assessment-only arm. For the 1:20 and 1:40 dilutions, both the Group x Time and the Group x Time x Stage interactions were significant, and approached significance for the 1:80 dilution (see Table 1).

Within-subjects contrasts and examinations of group means showed a similar pattern of anti MUC-1 antibody response over time for 1:20, 1:40, and 1:80 dilutions, as indicated in the three panels for Figure 2. Prior to randomization, women in both groups yielded similar anti MUC-1 antibody responses. At four months, when standard chemotherapy treatment was being received by the majority (85%) of the sample, antibody levels declined in both study arms. It is known that chemotherapy affects both B cells that secrete the antibody as well as helper T cells which help B cell antibody production. The number of women receiving chemotherapy declined by the 8 month (22% of the entire sample) and 12 month (4% of the entire sample) assessments, and so it would be expected that there would be some leveling off at 8 or 12 months of the antibody response decline observed at 4 months. Indeed, the latter scenario was observed for the patients in the Assessment only arm. In contrast, the patients in the Intervention arm promptly recovered anti-MUC1 antibody responses. As predicted, within-subjects contrasts showed that MUC-1 levels for patients in the Intervention arm significantly rebounded by the 8-month and 12-month assessments than was the case for patients in the Assessment only arm. Specifically, MUC-1 levels remained significantly lower for the Assessment only arm than for the Intervention arm at 8 months for the 1:20 dilution [$F(1,77) = 4.29$, $p < .05$] and at 12-months for the 1:20 dilution [$F(1,77) = 4.14$, $p < .05$] and the 1:40 dilution [$F(1,77) = 3.96$, $p < .05$]. For the 1:40 dilution, the within-subjects contrast at 8 months approached significance [$F(1,77) = 3.59$, $p = .06$].

Regarding the Group x Time x Stage effects, at eight months, this effect was significantly stronger in Stage III patients for the 1:40 dilution [$F(1,77) = 3.99$, $p < .05$]; these data for Stage II and Stage III patients are displayed in the two panels in Figure 3. The remaining Group x Time x Stage contrasts were not significant.

The majority of the anti-MUC1 antibody response in breast cancer patients is of the IgM isotype which reflects the tandemly repeated nature of B cell epitopes along the MUC1 polypeptide

core[28]. Some patients, however, also develop low level IgG responses. We performed isotype specific ELISA on the subset of serum samples to test for the possibility that recovery of antibody responses may also have been accompanied by isotype switching and presence of new isotypes. We found that this was not the case. The antibody isotypes present at the 8 and 12 month assessments were the same as those found pretreatment (data not shown).

DISCUSSION

> In breast cancer "a paradoxical situation exists: Optimism results from emerging insights into the basic genetic and biochemical mechanisms of breast cancer. Frustration grows from the poor record of the past in terms of extending life and improving the quality of life" (Institute of Medicine, National Academy of Science[3]; pg. 1).

The psychosocial burdens of cancer are notable in number, severity, and scope (see 29-31 for reviews), and finding strategies to reduce stress and prevent deterioration in quality of life (QoL) has become an important national research objective in cancer control[4]. Our data show that a psychological/behavioral intervention can result in reductions in important symptoms--depressed affect and stress, as indexed by cortisol lowering. While improvements in psychological outcomes for cancer patients have been demonstrated (see 12 or 32 for reviews), concurrent documentation by reduction of an HPA axis response has not been shown. Changes in the behavioral and psychological aspects of stress and depression are important, as recent data suggest that stress and depressive symptoms are among the ones that lead women with breast cancer to seek out psychological therapies and stress reduction techniques (e.g. relaxation) for assistance in coping during the first year following diagnosis[33].

That the intensive (weekly) phase of the intervention was associated with a lowering of a HPA axis stress response is an important finding. While the design of this experiment can not identify what component of the intervention led to the lowering of cortisol, per se, it is likely that training the patients in the use of progressive muscle relaxation as a behavioral coping strategy was important to reduce feelings of bodily tension and stress and/or cope with unpleasant treatment side

effects (e.g. fatigue, sleep difficulties, nausea, vomiting, pain). In fact, we examined the correlation between the initial cortisol values and the womens' reports of their weekly frequency of relaxation practice, and the correlation was .39, indicating that women with initially higher cortisol levels also reported more regular use of relaxation training. This particular method, a specified sequence of tension-release cycles for large muscle groups of the body paired with instructions to focus on the bodily sensations of relaxation[34], was selected because of its differential effectiveness in producing positive psychological and physiologic effects (e.g. reductions in heart rate, respiration or EMG assessed muscle tension) in other groups with health difficulties. For example, the use of biofeedback assisted relaxation training with other patient groups (e.g., muscle tension feedback with Type II diabetics[35] or persons with essential hypertension[17]) has resulted in significant decreases in urinary/plasma cortisol, and such decreases have been sustained for as long as one year following training[18]. Conversely, when cortisol remains elevated it has been associated with adverse health conditions (e.g., atherosclerosis[36], cognitive deficits[37]) in both stressed and non stressed adults.

To our knowledge, these are the first experimental data to demonstrate a connection between an endocrine and a disease specific immune response in the context of a psychological intervention for cancer patients. Our results show that the ability to activate immune memory cells and/or prime naïve cells is present in the context of intervention, but much lower or absent in the assessment only group. What best correlates with this ability are levels of cortisol measured in the two groups. The Assessment only group maintained initially high levels of this stress hormone and appeared unable to recover its anti-MUC1 antibody responses. Cortisol, like other glucocorticoids, is known to induce apoptosis of mammalian T and B cells[38, 39] and inhibit cytokine production of other leukocytes[40]. Stress paradigms with animals suggest that endocrine factors released during stress modulate leukocyte trafficking and result in the redistribution of leukocytes between the blood and other immune compartments[41]. Such reductions in function and redistribution would be expected to significantly effect the ability of the immune system to respond to potential or ongoing immune challenges.

Considering the interactions between differential levels of cortisol and the immune response found here, the observed differential anti-MUC1 antibody response between the Intervention and Assessment only arms at 8 and 12 months would be predicted. Specifically, the presence of high levels of cortisol during the chemotherapy period (primarily from the initial to the 4 month assessment) for the Assessment only patients would be expected to contribute to greater damage to T and B cells, and the continued presence of cortisol post chemotherapy would slow down cell recovery. Higher levels of cortisol in the period immediately after chemotherapy would have a profound, long term effects, even if cortisol levels eventually return to normal. This continuing negative effect would be predicted to occur because there is a narrow window after chemotherapy during which antigen (MUC1) is present in circulation and could elicit antibody responses. If during that time, the intervention results in a reduction in cortisol, T and B cell recovery will coincide with that window. In contrast, if cortisol lowers slowly (or only minimally), T and B will not encounter their specific antigen and no antibody will be produced (In fact, mean cortisol levels for the Assessment only group remained at the initial baseline level or even increased further, rather than decline).

The major anti-MUC1 antibody response found in breast cancer patients is IgM. Production of IgM antibody is a result of a direct B cell activation on tandemly repeated epitopes along the MUC1 polypeptide core and is considered to be relatively helper T cell independent[28]. In addition, some IgG responses have been identified that depend on the activation of helper T cells specific for MUC1[42]. Reduction of anti-MUC1 antibody levels during and post chemotherapy in both groups of patients is a consequence of a direct lytic effect of chemotherapy on activated T and B cells. As noted above, the recovery of anti-MUC1 antibody responses in patients in the Intervention arm can be attributed to activation of memory B and T cells that have survived chemotherapy, and/or priming of newly emerging T and B cells on the circulating MUC1 antigen, expected to be present in the serum post tumor destruction[43,44]. These two events would be expected to contribute unequally in Stage II and Stage III patients and likely account for their differential anti MUC1 antibody responses (see Figure 3). Specifically, the memory cells are

expected to be more responsible for recovering and maintaining anti-MUC1 antibody in Stage II patients. The tumor burden in these patients is smaller, and post surgery and chemotherapy there should be low amounts of MUC1 antigen present in circulation. These amounts may be sufficient to activate memory B cells that require very little antigen, but not to prime additional naïve B cells that require a much higher antigen dose. In Stage III patients, however, higher levels of MUC1 would be expected to be present due to more advanced disease, the activation of memory cells, and, in turn, the new naïve B cells can be recruited into the response. Such circumstances can account for the stronger recovery of antibody responses in Stage III patients.

There were several advantages of using anti MUC1 antibody as the immune outcome of this intervention. First, quantitative measures or even other functional assessments (e.g. NK cell lysis, T or B cell blastogenesis) provide a transient assessment of the stress environment rather than an adaptive (i.e. memory) response of the immune system. Importantly, T cell recognition of antigen through the T-cell receptor is the basis of a range of immunological phenomena, including T-cell helper and suppressor activity, cytotoxicity, and, possibly, NK cell activity. Second, the MUC1 response is specifically relevant to breast cancer, and moreover, the strength of the response is related to clinical outcomes (i.e., the disease free interval and overall survival[24]). Third, with the disease specificity of the MUC1 response, it serves as a plausible marker of an overall anti-tumor response in the patient.

Studies have shown improved survival for cancer patients following psychological interventions[45,46], though the mechanism(s) for these effects are unclear. Whether or not the immune responses shown here will have parallel clinical import remains to be determined, although the 12 month recurrence/survival data are in the hypothesized direction. Specifically, by the 12-month assessment, eight subjects had dropped from the study (3 Intervention, 5 Assessment only), five subjects had recurred or recurred and died from their disease (1 Intervention, 4 Assessment only), and 2 subjects had died of other causes (1 Intervention, 1 Assessment only). The convergence of psychologic, endocrine, and immune effects shown here provides an important empirical foundation for clarifying the biobehavioral mechanisms in the examination of the

relationship between stress and cancer outcomes.

METHODS

Patient eligibility and data collection

Participants were 115 women who had been diagnosed and surgically treated for Stage II (84%) or III (16%) invasive breast cancer. At the time of accrual, women were from 14 to 101 days (M = 37 days, SD = 17) post surgery and had not yet begun their standard adjuvant therapy. The majority of participants (78%) were being treated at a NCI designated, University affiliated Comprehensive Cancer Center and the remainder (22%) were receiving treatment at local community hospitals.

Sociodemographic description of the sample revealed the following characteristics: racial distribution (88% Caucasian, 10% African American, 2% Hispanic); age (M = 51 years, SD =11; range 31 to 84 years); marital status (65% married, 26% divorced/widowed, 9% never married); education level (M = 15 years); employment status (65% employed full or part time; 35% unemployed outside the home or retired); and, annual personal income (M = $28,000, range of $2-$110,000).

Recruited consecutively from mid 1994 to early 1997, all women came to the General Clinical Research Center at the university or the outpatient breast cancer center for the collection of psychological, behavioral, and medical data, and a 60ml blood draw. Assessments were conducted between 8:00 am and 12:00 pm to reduce diurnal variability. After the initial assessment, patients were randomized between Intervention and assessment (n = 57) vs. Assessment only (n = 58) arms. Randomization was stratified by prognostic (i.e. tumor size/number of lymph nodes, estrogen receptor status, menopausal status) and psychosocial (i.e., presence/absence of a significant other) variables. All patients began their standard adjuvant cancer therapy following accrual and initial assessment, and were then reassessed at 4, 8, and 12 months. From the time of the initial to the 4 month assessment, 85% of the entire sample received chemotherapy. From the time of the 4 to the 8 month assessment, 22% of the entire sample received chemotherapy, and between the 8 and 12 month assessment 4% of the sample received

chemotherapy.

Intervention protocol

The intervention was conducted in an outpatient psychological clinic in the Department of Psychology on the university campus. A biobehavioral model[27] provided the conceptual framework for the intervention. Six components, each with specific intervention strategies, were included: 1) stress reduction (i.e. training in progressive muscle relaxation, conceptualization for the relationship between stress and health); 2) enhancing quality of life (i.e. identifying sources of social support and improving support from friends and family; assertive communication; coping with body changes and enhancing sexuality; problem solving for cancer-related difficulties, e.g. fatigue); 3) increasing positive health behaviors (i.e. beginning/maintaining moderate exercise; breast cancer-relevant dietary/nutrition changes, e.g. increased fiber and lower fat intake); 4) decreasing negative health behaviors (i.e. reduce smoking, alcohol consumption); 5) improving compliance (e.g. seeking additional information about cancer treatments; assertive communication with health care providers); and, 6) support offered/received by therapists and group members.

The intervention was delivered in a group format, consisting of a cohort of 8-12 women and 2 Ph.D. clinical psychologists as therapists (B.A. and D. G.-K.). A single intervention cycle was 26 1.5 hour sessions (18 weekly + 8 monthly sessions) for a total of 39 therapy hours delivered over a 12 month period; six cohorts of patients completed the intervention. Reliability of the treatment procedures was insured by having the therapists follow a session-by-session written manual, provision of a modified therapy manual to the patients, and weekly meetings of the therapist team to review the previous session, rate the topic coverage, and prepare for the next session. Treatment "dose" to the women was documented; in session attendance was documented. Session absences were followed within 3 days by a telephone call to the woman from one of the therapists to provide coverage of the group session, including discussing the content of the week's intervention session, assigning the intervention 'homework,' and updating the patient on the concerns of the other group members.

Assessment only patients came to the Clinical Research Center (CRC) at the University

Hospital or the outpatient breast cancer center for the assessment interviews and blood draw. Women were reimbursed for parking ($4) and paid a modest fee ($20) for their time and effort for each assessment. Identical assessment procedures were followed for the patients randomized to the intervention arm.

Measures and Assays

Psychological: depressive symptoms. We employed the short form (IOWA version[47]) of the Center for Epidemiological Studies Depression Scale (CES-D)[48, 49]. This is a standardized self-report questionnaire used to identify current symptoms of depression, with an emphasis on depressed affect. The CES-D short form consists of 11 items (e.g. "I felt everything I did was an effort," "I feel sad") rated on a 3 point Likert scale from 'hardly ever or never" to "much or most of the time." Women responded based on their feelings during the previous week. Total scores can range from 0 to 22 with higher scores reflecting greater symptoms. Unlike other measures of depressive symptoms, the CES-D is relatively unaffected by physical symptoms and is, therefore, commonly used in research with medical patients[50]. Internal consistency reliability was .74.

Endocrine: Plasma cortisol. Cortisol was measured using chemiluminescence technology (Nichols Institute, San Juan Capistrano, CA.). The sensitivity of the assay (0.8 ug/dl) was adequate to measure cortisol in each sample. Large cortisol assays (usually 2 cohorts of 20 Ss each with all four assessments) were run to eliminate interassay variation. The inter and intra assay coefficient variations of the assay are less than 8%.

Immune: MUC1-specific antibodies. Venous blood was collected in 10 ml green top (heparin) tubes and mixed to avoid clotting. Tubes were then centrifuged at 1700 rpm for 10 minutes in Beckman GS-6R Centrifuge. With sterile technique, 5 ml of plasma was then removed, placing 1 ml into each of three cryovials and 2 ml. into one cryovial. Tubes were frozen at -20° C and then subsequently moved for storage at -70° C.

Microtiter plates (Immulon 4, Dynatech Labs) were coated with synthetic MUC1 peptide, 40 amino acids in length, corresponding to two tandem repeats from the MUC1 polypeptide core [(PDTRPAPGSTAPPAHGVTSA) x 2]. Each well was coated with 1ug of peptide dissolved in

phosphate buffered saline (PBS). Following an overnight incubation at 40° C, the plates were washed twice with PBS and to each well was added 100 ul of a 2.5% solution of bovine serum albumin (BSA, Sigma Chemical Co., St. Louis, MO) in PBS to block uncoated plastic surfaces in the wells. This blocking step was performed for 1 hour at 22° C. The plates were then inverted to remove the blocking reagent (BSA-PBS). Various dilutions of patients' plasma samples were made in the blocking reagent (2.5% BSA-PBS) and 50 ul were added into the wells. Each dilution was tested in triplicate wells. An exact replica microtiter plate was prepared at the same time which was only "mock" coated with PBS without MUC1 peptide, blocked with BSA-PBS, and reacted with serial dilutions of the plasma samples. This plate served as a control for nonspecific binding.

Incubation of the peptide-coated and the control plates was for 1 hour after which the plates were washed 5 times with PBS containing 0.01% Tween 20 detergent. Each well then received 50ul of the secondary antibody, alkaline phosphatase conjugated goat anti-human Ig (anti IgG, IgM and IgA) (Sigma, #A3313), diluted 1:1000 in BSA-PBS. Following a 1 hour incubation, the plates were again washed 5 times with PBS-0.01% Tween. Each well then received 100ul of phosphatase substrate (Sigma #3104), at the concentration of 3ug/ml, diluted in 0.5mM MgCl2, 0.05M Na2CO3. The reaction was terminated after 1 hour by adding 50ul of 0.05 M NaOH, and absorbency was measured at 492nm. The OD values from the wells on the control plate that did not receive MUC1 peptide were subtracted from the values in test wells containing peptide to determine antibody specific reactivity. These procedures were followed after the collection of the last serum samples; all time points for all subjects were run in the same assay. The assays were run multiple times.

Data analyses

Data were evaluated by intention to treat. We predicted that the psychological/behavioral intervention would yield positive psychological, endocrine, and immune effects for patients randomized to the intervention arm, in contrast to the effects for the patients randomized to the assessment only arm. We expected these responses to be manifest across time, with both groups having equivalent responses at the initial (pretreatment) assessment, with group differences

emerging across the 4-, 8- and/or 12 month assessments. The period from the initial to the 4 month assessment was potentially the most stressful as it coincided with the delivery of 4 to 8 cycles of adjuvant chemotherapy for the majority (85%) of the patients in the study. As the intervention was intensive during the first 4 months (i.e. weekly intervention sessions), we anticipated the greatest reductions in stress (i.e. cortisol) and improvements in psychological responses (i.e. depressive symptoms) during the difficult, initial to 4 month period. We anticipated some lessening of stress reduction or psychological improvements as the patients in the intervention arm shifted from the weekly to the monthly intervention sessions during the 4 to 12 month follow ups, as maintenance of psychological/behavioral effects is difficult to achieve[51]. We predicted a replication of the general effects of the intervention across stage, but we anticipated that intervention effects might be strongest for women with stage III disease, as effectiveness of psychological interventions is robust for individuals with more extensive disease[12].

For all measures--psychological, endocrine, and immune--a repeated measures analysis of variance (ANOVA) model was used. The primary hypothesis was tested by examining the interaction between Group x Time, with Group (Intervention vs. Assessment only) and Stage (II vs. III) as between subjects factors and Time (initial, 4-, 8-, and 12 months) as a within (repeated measures) factor. Finally, as the mucin assay was conducted across three target: cell ratios, 1:20, 1:40, and 1:80, we ran an ANOVA model for each, with the expectation that significant interactions should, in general, be replicated across the cell ratios. The latter strategy can demonstrate the reliability of an intervention effect on the antibody response.

Acknowledgments

Supported by grants from the American Cancer Society (PBR-89), the Longaberger Company-American Cancer Society Grant for Breast Cancer Research (PBR-89A), the U.S. Army Medical Research Acquisition Activity Grants (DAMD17-94-J-4165 and DAMD17-96-1-6294), the National Institutes of Mental Health (R01 MH51487), the General Clinical Research Center (MO1-RR0034), the Ohio State University Comprehensive Cancer Center Core Grant (CA16058), and the Department of Psychology and the College of Social and Behavioral Sciences at The Ohio State University.

We thank the participants for their assistance. In addition, we thank the following individuals for their contributions: Nicole Chaput, Angela Collier, Katheryn Pingel, Elizabeth Street, Jessica Walker, JoAnne Lester and Beth Putz for accrual and conducting the psychological and medical assessments; Marilyn Welt for blood cell preparation for the immune assay; and, Susan Moseley for conducting the cortisol assay.

REFERENCES

1. Andersen, B.L., Anderson, B., deProsse, C. Controlled prospective longitudinal study of women with cancer: II Psychological outcomes. Journ. Consul. Clin. Psych. 57, 692-697 (1989).

2. Moyer, A. & Salovey, P. Psychosocial sequelae of breast cancer and its treatment. Ann. of Behav. Med. 18(2), 110-125 (1996).

3. Institute of Medicine. Strategies for managing the breast cancer research program: A report to the U.S. Army Medical Research and Development Command. National Academy Press, Washington, D.C. (1993).

4. National Cancer Institute. Cancer Prevention and Control Reports. U.S. Government Printing Office, Washington, DC. (1997).

5. Chrousos, G.P., & Gold, P.W. The concepts of stress and stress system disorders: Overview of; physical and behavioral homostasis. J.A.M.A. 267, 1244-1252 (1992).

6. Gold, P.W., Goodwin, F. K., & Chrousos, G.P. Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress (Part I). N. Engl. J. Med. 319, 348-353 (1988).

7. Gold, P.W., Goodwin, F. K., & Chrousos, G.P. Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress (Part II). N. Engl. J. Med. 319, 413-420 (1988).

8. Herbert TB, Cohen S. Depression and immunity: A meta-analytic review. Psychol. Bull. 113, 472-486 (1993).

9. Herbert, T.B., Cohen, S. Stress and immunity in humans: A meta-analytic review. Psychosom. Med. 55, 364-379 (1993).

10. Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. Stress and immune responses following surgical treatment of regional breast cancer. J. Nat. Cancer Inst. 90 (1), 30-36 (1998).

11. Levy, S.M., Herberman, R.B., Maluish, A.M., Schlein, B., Lippman, M. Prognostic risk

assessment in primary breast cancer by behavioral and immunological parameters. Health Psychol. 4, 99-113 (1985).

12. Andersen, B.L. Psychological interventions for cancer patients to enhance the quality of life. J. Consult. Clin. Psychol. 60, 552-568 (1992).

13. Fawzy, F.I., Cousins, N., Fawzy, N.W., Kemeny, M.E., Elashoff, R., Morton, D. A structured psychiatric intervention for cancer patients: I. Changes over time in methods of coping and affective disturbance. Arch. Gen. Psychiatry 47, 720-725 (1990).

14. Fawzy, F.I., Kemeny, M.E., Fawzy, N.W., Elashoff, R., Morton, D., Cousins, N., Fahey, J.L. A structured psychiatric intervention for cancer patients: II. Changes over time in immunological measures. Arch. Gen. Psychiatry 47, 729-735 (1990).

15. McKinney, C.H., Antoni, M.H., Kumar, M., Tims, F.C., & McCabe, P.M. Effects of guided imagery and music (GIM) therapy on mood and cortisol in healthy adults. Health Psychol. 16, 390-400 (1997).

16. McGrady, A.,V., Yonker, R., Tan, S.Y., Fine, T.H. The effect of biofeedback-assisted relaxation training on blood pressure and selected biochemical paramentes in patients with essential hypertension. Biofeedback Self. Regul. 6, 343-353 (1981).

17. McGrady, A., Woerner, M., Bernal, G. A.A., & Higgins, J.T. Effect of biofeedback-assisted relaxation on blood pressuire and cortisol levels in normotensives and hypertensives. J. Behav. Med. 10, 301-310 (1987).

18. McGrady, A.,V., Nadsady, P.A., & Schumann-Brzezinski, C. Sustained effects of biofeedback-assisted relaxation training in essential hypertension. Biofeedback Self. Regul. 16, 399-411 (1991).

19. McGrady, A.,V., Conran, P., Dickey, D., Garman, D., Farris, E., & Schumann-Brzezinski, C. The effects of biofeedback-assisted relaxation training on cell mediated immunity, cortisol, and white blood cell count in healthy adults subjects. Biofeedback Self. Regul. 6, 343-353 (1992).

20. Cohen, S., Tyrrell, D.A., & Smith, A.P. Psychological stress and susceptibility to the common cold. N. Engl. J. Med. 325, 606-612 (1991).

21. Kiecolt-Glaser, J.K., Glaser, R., Gravenstein, S., Malarkey, W.B., & Sheridan, J.S. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc. Nat. Acad. Sci., 93 (1993).

22. Henderson, R.A., & Finn, O.J. Human tumor antigens are ready to fly. Adv. Immunol. 62, 217-256 (1996).

23. Ciborowski, P., Hiltbold, E.M., Barratt-Boyes, S., Finn, O.J. MUC1 mucin as a tumor antigen in breast cancer. In Breast Cancer: Molecular genetics, pathogenesis and therapeutics, ed. Bowcock, A.M., Humana Press, Totowa, New Jersey, pp 453-468 (1999).

24. Von Mensdorff-Pouilly, S., Gourevitch, M.M., Kenemans, P., Verstraeten, A.A., Litvinov, S.V., van Kemp, G.J., Meijer, S., Vermorken, J., Hilgers, J. Humoral immune response to polymprphic epithelial mucin (MUC-1) in patients with benign and malignant breast tumors. Eur. J. Cancer 32, 1325-1331 (1996).

25. Jerome, K.R., Lomenech, N., & Finn, O.J. Tumor-specific cytotoxic T cell clones from patients with breast and pancreatic adenocarcinoma recognize EBV-immortalized B cells transfected with polymorphic epithelial mucin complementary DNA. J. Immunol. 151, 1654- 1657 (1993).

26. MacLean, G.D., Reddish, M.A., & Longenecker, B.M. Pre immunotherapy serum CA27.29 (MUC1) mucin level following active specific immunotherapy of metastatic adenocarcinoma patients. J. Immunother. 19, 70-78, (1997).

27. Andersen, B.L., Kiecolt-Glaser, J.K., Glaser, R. A biobehavioral model of cancer stress and disease course. Am Psychol. 49, 389-404 (1994).

28. Kotera, Y., Fontenot, D.J., Pecher, G., Metzgar, R.S., Finn, O.J. (1994) Humoral immunity against a tandem repeat epitope of human mucin MUC-1 in sera from breast, pancreatic and colon cancr patients. Cancer Res. 54:2856-2860.

29. Andersen, B.L. Surviving cancer. Cancer 74, 1484-1495 (1994).

30. American Cancer Society. Proceedings of the working conference on methodology in behavioral and psychosocial cancer research --1983. Cancer, 53 (Suppl. 10), 2217-2384, (1984).

31. American Cancer Society. Proceedings of the second workshop on methodology in

behavioral and psychosocial cancer research --1989. Cancer, 67 (Suppl. 1), 765-868, (1991).

32. Meyer, T.J., & Mark, M.M. Effects of Psychosocial interventions with adult cancer patients: A meta-analysis of randomized experiments. Health Psychol. 14, 101-108 (1995).

33. Burstein, H.J., Gelber, S., Guadagnoli, E., & Weeks, J.C. Use of alternative medicine by women with early-stage breast cancer. N. Engl. J. Med. 340, 1733-1739 (1999).

34. Bernstein, D.A., & Borkovec, T. D. Progressive relaxation training. Research Press, Champaign, IL. (1973).

35. Surwit, R.S., & Feinglos, M.N. Relaxation-induced improvements in glucose tolerance is associated with decreases in plama cortisol. Diabetes Care 7, 203-204 (1984).

36. Troxler, R.G., Sprague, E.D., Albanese, R.A., Fuchs, R., & Thompson, A.J. The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. Atherosclerosis 26, 151-162 (1977).

37. Lupien, S., Lecours, A.R., Lussier, I., Schwartz, G., Nair, NP.V., & Meaney, M.J. Basal cortisol levels and acognitive deficits in human agian. J. Neurosci. 14, 2893-2903 (1994).

38. Wyllie, A.H. Glucocorticoid-induced thymocyte apoptosis is associated with endogenous endonuclease activation. Nature, 284, 555-556 (1980).

39. Munck, A. and Crabtree, G.R. Glucocorticoid-induced lymphocyte death, In Cell death in biology and pathology, ed. I.D. Bowen and R.A. Lockshin, Chapman and Hall, London, pp. 329-359 (1981).

40. Munck, A. and Guyer, P.M. Glucocorticoids and immune function. In Psychoneuroimmunology, 2nd. Ed., ed. R.Ader, D.L. Felten and N. Cohen, Academic Press, San Diego, pp. 447-474 (1991).

41. Dhabhar, F.S., Miller, A.H., McEwen, B.S., & Spencer, R.L. Effects of stress on immune cell distribution: Dynamics and hormonal mechanisms. J. Immunol. 154, 5511-5527 (1995).

42. Jerome, K.R., Barnd, D.L., Boyer, C.M., Taylor-Papadimitriou, J., McKenzie, I.F.C., Bast, Jr. R.C., Finn, O.J. Cytotoxic T lymphocytes derived from patients with breast adenocarcinoma recognize an epitope present on the protein core of a mucin molecule preferentially

expressed in malignant cells. Cancer Res. 51, 2908-2916 (1991).

43. Hilkens, J., Kroezen, V., Bonfrer, J.M.G., De Jong-Bakker, M., Bruning, P.F. MAM-6, a new serum marker for breast cancer monitoring. Cancer Res. 46, 2582-2587 (1986).

44. Hayes, D.F., Sekine, H., Ohno, T., Abe, M., Keefe, K., Kufe, D.W. Use of a murine monoclonal antibody for detection of circulating plasma DF3 antigen levels in breast cancer patients. J. Clin. Invest. 75, 1671-1678 (1985).

45. Fawzy, F.I., Fawzy, N.W., Hyun, C. S., Gutherie, D., Fahey, J.L., & Morton, D. Malignant melanoma: Effects of a early structured psychiatric intervention, coping, and affective state on recurrence and survivial six years later. Arch. Gen. Psychiatry 50, 681-689 (1993).

46. Spiegel, D., Bloom, J.R., Kraemer, H.C., & Gottheil, E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 2 (8668), 888-891 (1989).

47. Kohout, F.J., Berkman, L.F., Evans, D.A., & Cornoni-Huntley, J. Two shorter froms of the CES-D depression symptoms index. J. Aging Health 5, 179-193 (1993).

48. Comstock, G.W., & Helsing, K.J. Symptoms of depression in two communities. Psychol. Med. 6, 551-563 (1976).

49. Radloff, L.S. The CES-D scale: A self-report depression scale for research in the general population. App. Psychol. Meas. 1, 385-401 (1977).

50. Devins, G.M., Orme, C.M., Costello, C.G., Binik, Y.MN., Frizzell, B., Stam, H.J., & Pullin, W.M. Measuring depressive symptoms in illness populations: Psychometric properties of the Center for Epidemiologic Studies of Depression (CES-D) Scale. Psychol. Health 2, 139-156 (1988).

51. Prochaska, J.O., Velicer, W.F., Rossi, J.S., Goldstein, M.G., Marcus, B.H., Rokowski, W., Fiori, C., Larlow, L.F., Redding, C.A., Rosenbloom, D., & Rossi, S.R. Stages of change and decisional balance for 12 problem behaviors. Health Psychol. 13, 39-46 (1994).

Table 1 Analysis of Variance Interaction Results For MUC1 Across Three Dilutions

Within subjects				
F	df	1:20	1:40	1:80
Group x Time	3	4.30*	3.56*	2.61 [a]
Group x Time x Stage	3	3.72*	3.67*	3.01[a]
Within-group error	231	(.260)	(.047)	(.028)

Note: Values enclosed in parentheses represent mean square errors.

* $p < .05$

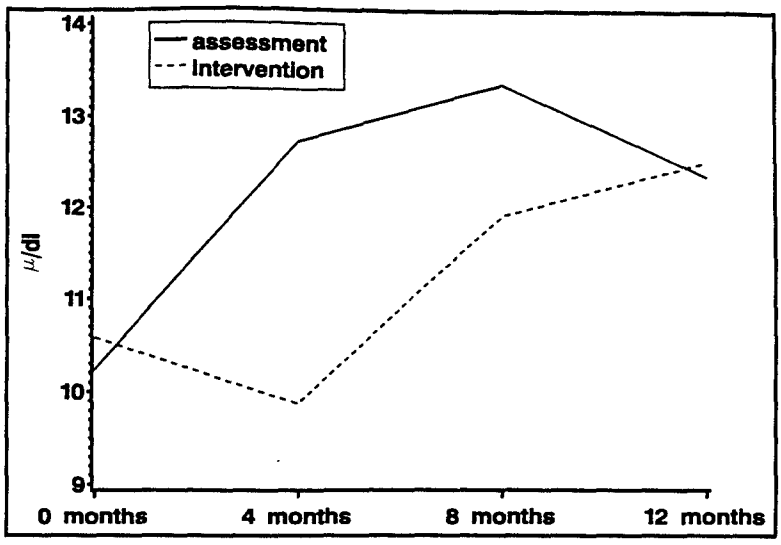
[a] $p < .10$

Figure Captions

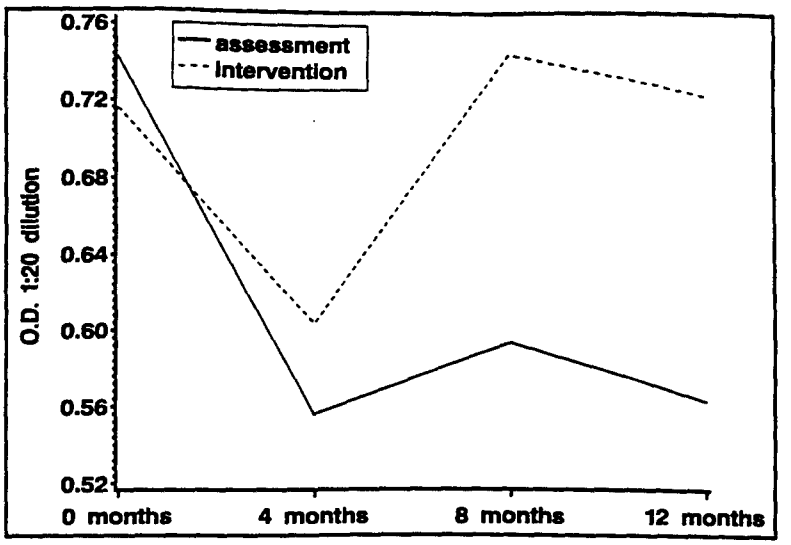
Figure 1. Mean cortisol levels for the Intervention and Assessment only study arms across Time for initial (0), 4-, 8-, and 12-month assessments. The figure illustrates the Group x Time interaction, indicating significant group differences over time. Specifically, cortisol levels for patients in the Intervention arm showed a significantly greater decrease from 0 to 4 months than cortisol levels for patients in the Assessment-only arm.

Figure 2. Mean anti-MUC-1 antibody levels for 1:20 (top, a), 1:40 (middle, b), and 1:80 (bottom, c) dilutions for Intervention and Assessment only study arms across Time for initial (0), 4-, 8-, and 12-month assessments. Figures illustrate Group x Time interactions at 1:20 ($p < .05$), 1:40 ($p < .05$), and 1:80 ($p < .10$). Specifically, anti-MUC-1 antibody levels for patients in the Intervention arm showed a significantly greater increase in their anti-MUC1 antibody response from 0 to 8 months and 0 to 12 months than did patients in the Assessment only arm.

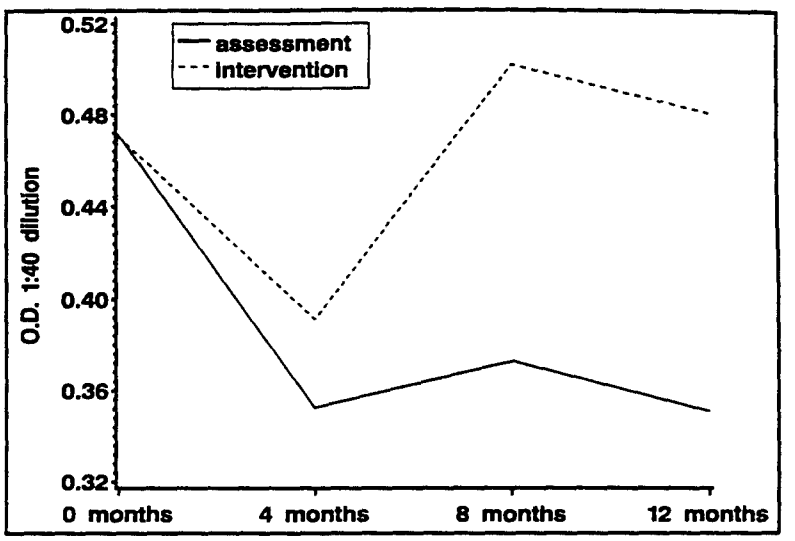
Figure 3. Mean anti-MUC-1 antibody levels for the 1:20 dilution for Intervention and Assessment only study arms across Time for initial (0), 4-, 8-, and 12- month assessments for patients with Stage II (top) versus Stage III (bottom) disease. Figures illustrate Group x Time x Stage interaction ($p < .05$). Specifically, the 1:40 dilution shows a significantly larger increase in anti-MUC-1 antibody response levels from 0 to 12 months for the Intervention arm patients than for the Assessment-only arm patients. This effect (see Fig. 2 above) can be seen most clearly at this dilution with the Stage III patients.


assessment
Intervention
14
13
12
11
10
9
µ/dl
0 months
4 months
8 months
12 months

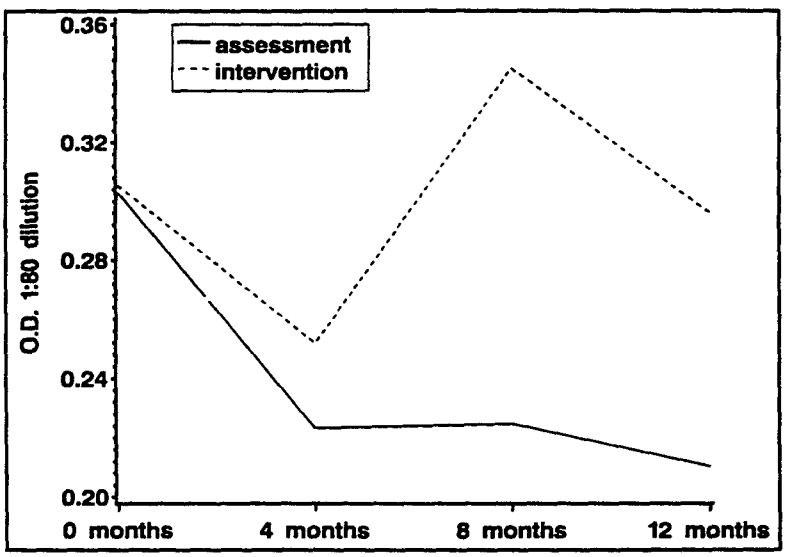
a.


assessment
intervention
O.D. 1:20 dilution
0.76
0.72
0.68
0.64
0.60
0.56
0.52
0 months
4 months
8 months
12 months

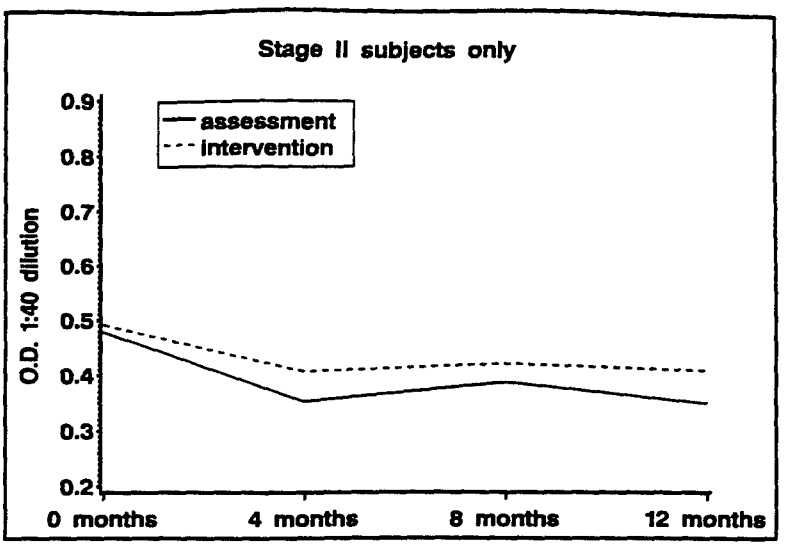
b.


assessment
intervention
O.D. 1:40 dilution
0.52
0.48
0.44
0.40
0.36
0.32
0 months
4 months
8 months
12 months

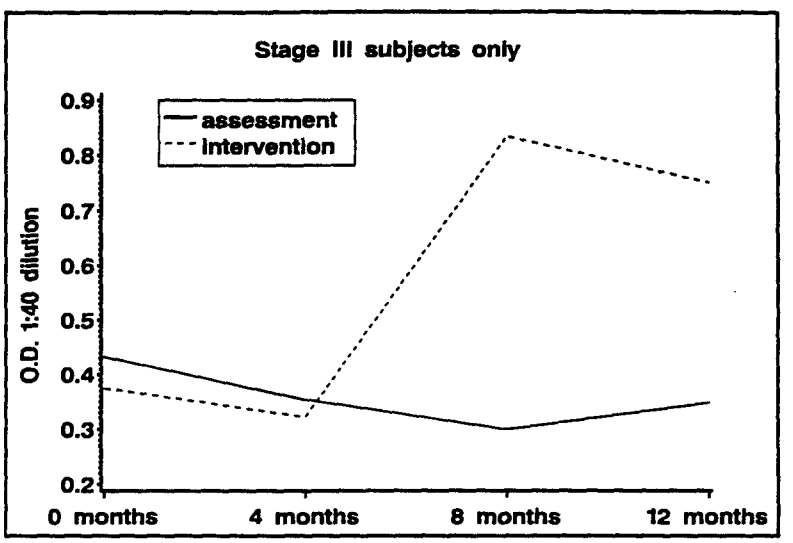
c.


assessment
intervention
O.D. 1:80 dilution
0.36
0.32
0.28
0.24
0.20
0 months
4 months
8 months
12 months

a.


Stage II subjects only
assessment
intervention
O.D. 1:40 dilution
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0 months
4 months
8 months
12 months

b.


Stage III subjects only
assessment
intervention
O.D. 1:40 dilution
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0 months
4 months
8 months
12 months

Appendix C

- Unpublished Data -

Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment

Deanna M. Golden-Kreutz, Mary Elizabeth Courtney,

Vicki G. DiLillo, and Barbara L. Andersen

The Ohio State University

Key words: Stress, depressive symptoms, breast cancer

Abstract

The relationship of objective stressors (life events) and subjective (perceived) stress to depressive symptoms was examined. These relationships were examined using a clinically relevant paradigm, stressed individuals who were vulnerable to the experience of depressive symptoms, namely women recently diagnosed and surgically treated for breast cancer. Analyses controlled for alternative hypotheses including: sociodemographic, disease, and personality factors. Using Hierarchical Multiple Regression, 51% of the variance in depressive symptoms was predicted, accounted for by the control variables (race, neuroticism), objective stressors (major financial difficulty and major conflict with children/grandchildren), subjective event stress (cancer stress; IES), and subjective global stress (PSS-10). An examination of the squared semipartial correlations indicated that perceived stress (10%), cancer stress (8%), and race (1%) accounted for significant unique variance in the final model. While "stress" measures are correlated, these findings indicate that subjective measures of stress were uniquely better predictors of depressive symptoms than objective measures. Further, a global perception of stress was a stronger predictor than perceived stress for a specific event. Implications for the use of such measures with stressed populations, who are often vulnerable to other comorbid difficulties such as depression, are discussed.

Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment

Stress, whether measured objectively or subjectively, is associated with poor psychological and physical outcomes across a variety of groups (e.g., college students and adults in community smoking cessation program: Cohen, Kamarck, & Mermelstein, 1983; adult psychiatric patients: Hewitt, Flett, & Mosher, 1992; highway patrol officers: Hills & Norvell, 1991). While studies may include both objective and subjective measures of stress, few studies have examined their relative associations to outcomes (Cohen et al., 1983; Cohen & Williamson, 1986; Hills & Norvell, 1991; Pbert, Doerfler, & DeCosimo, 1992). Such comparisons would be important because an examination of the "predictive validities of objective and subjective stress measures" would clarify the role of perceptions in the relationship between stress and outcomes (e.g., psychological functioning; p. 386, Cohen et al., 1983). The present study is an examination of the relative explanatory power of three different types of stress measures in relation to depressive symptomatology. This examination was conducted using an important and naturally occuring stressor - cancer diagnosis and treatment. Individuals are signficantly stressed at the time of diagnosis and treatment, and depressive symptoms are the most common affective symptoms reported (e.g., Derogatis et al., 1983; See Tope, Ahles, & Silverfarb, 1993, and van't Spiker, Trijsburg, & Duivenvoorden, 1997 for reviews).

Conceptualization and measurement of stress

The conceptualization and methodology in research on self-reported stress has evolved over the last 20 years (See Table 1 for an overview of the measures available). Early research on the psychological effects of stress arose from the notion that difficult life events (unemployment, death of a relative, etc.) are stressors (Cobb & Kasl, 1977; Stroebe, Stroebe, Gergen, & Gergen,

1982). Studies focused on the objective assessment of stress, the presence/absence, total number, or type of stressful life events experienced during a specified period of time (e.g., during the last year). Such measures did not involve evaluations, feelings, or cognitions associated with the events. These measures appeared important, as the data indicated that the number and/or type of life events were associated with psychopathology including depression (Finlay-Jones & Brown, 1981; Warheit, 1979), anxiety (Finlay-Jones & Brown, 1981; Manfro et al., 1996), anorexia nervosa (Horesh et al., 1995), and psychosis (Bebbington et al., 1993). Additionally, a greater number of events have been related to poorer health outcomes (Baum, Gatchel, & Schaffer, 1983; Dohrenwend & Dohrenwend, 1974; 1978; Holmes & Rahe, 1967).

Despite these data, objective measures were criticized as they did not account for individual differences in response to stressors. It was reasoned that a person's response to stressors is not based completely on the type or number of events, but also involves cognitive appraisal processes as well (Cohen et al., 1983; Lazarus & Folkman, 1984). For these latter processes, subjective measures of stress were introduced. Subjective measures assess perceptions of stress during a specific time period (e.g., the past week or month) and are of two basic types: event specific or global. Event specific measures ask the person how stressful a given situation (e.g., occupation) or event (e.g., bereavement, cancer diagnosis) is perceived to be. Event specific measures can be: 1) a one-item measure of how stressful a single event/situation is perceived, 2) a total score across items (stressors), or 3) a measure with several items assessing different aspects of a single event/situation. Alternatively, global subjective measures do not reference specific events/situations, but instead ask individuals if they perceive their lives as generally stressful.

When the differential predictive power of objective versus subjective measures have been

compared, subjective measures have consistently been better predictors of psychological and physical outcomes (Cohen et al., 1983; Martin, Kazarian, & Breiter, 1995; Pbert et al., 1992; Sarason, Johnson, & Siegel, 1978; Vinokur & Selzer, 1975). For example, Cohen and colleagues (1983) offered a global measure of preceived stress, the Perceived Stress Scale (PSS), contending that such a measure would provide a better measure of stress than would objective stressors or even subjective ratings of events. They raised three concerns with the other methods. First, the predictive power of subjective ratings of events relative to objective measures of events appeared to be small. Second, they suggested that people err in the attributions they make about their stress. For example, it is more common for individuals to associate stress with a current, identifiable event (e.g., recent death of relative, divorce) than with chronic circumstances (e.g., financial problems, marital distress). Third, they asserted that responses to an event are better reflected by global stress measures than stress associated with specific events or situations. For instance, a person's response to an event does not occur in isolation but in the context of other factors (socioeconomic status, personality, etc.) and, of course, all of these factors may contribute to one's perception of stress. Research has suggested global subjective stress ratings may be a better predictor of psychological outcomes than either objective or event specific measures of stressors (Cohen et al., 1983; Kuiper, Olinger, & Lyons, 1986; Martin et al., 1995; Pbert et al. 1992).

An example: Assessment of stress in cancer populations

Studies have examined life events as predictors of cancer risk (e.g., Cooper and Faragher, 1993; Ginsberg, Price, Ingram, & Nottage, 1996; Ramirez et al., 1989; Roberts, Newcomb, Trentham-Dietz, & Storer, 1996), but few studies have examined the relationship between life events and the stress of diagnosis and treatment. The available data suggest that an increased

number of recent life events are positively related to distress (Bukberg, Penman, & Holland, 1984; Grassi, Malacarne, Maestri, & Ramelli, 1997; & VanServellen, Sarna, Padilla, & Brecht, 1996).

Early studies documented acute distress experienced at diagnosis (e.g., Andersen, Anderson, & deProsse, 1989; Weisman & Worden, 1976), but contemporary studies suggest that cancer diagnosis and treatment may, in fact, constitute a "traumatic event" (4th ed; DSM-IV: American Psychiatric Association, 1994; Cordova et al., 1995; Andrykowski, Cordova, Miller, & Studts, 1998). As a result, existing measures of traumatic stress such as the Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979) have been modified for cancer populations (changing the word "event" on the original scale to "disease" or "cancer"). Much of the research examining cancer stress has, in fact, used the IES to examine the frequency or severity of trauma-related intrusive cognitions and avoidant behaviors, and their relationships to psychological outcomes (Baider & De-Nour, 1997; Cordova et al., 1995; Schwartz, Lerman, Miller, Daly, & Masny, 1995). There are consistent positive relationships between intrusive thoughts and severity of psychological distress (e.g., patients at high risk for cancer, Schwartz et al., 1995), and weaker or no relationship between avoidant thoughts/behaviors and psychological distress (breast cancer patients, Baider & De-Nour, 1997 and Cordova et al., 1995; parents of pediatric cancer patients, Hall & Baum, 1995).

In contrast to the use of subjective ratings of the cancer "event," fewer cancer studies have included globally perceived stress measures (Bull & Drotar, 1991; Schulz et al., 1995; Varni et al., 1994). One of these exceptions is a study by Varni and colleagues (1994) who found that higher perceived global stress predicted increased psychological distress (e.g., depression and anxiety) in adolescent survivors of pediatric cancer. In comparing the three methodologies, the research focus has been on objective stressors and subjective ratings of the cancer stressor, with fewer

studies examining subjective global stress.

A closer look at the stress of cancer diagnosis and treatment

The diagnosis and treatment of cancer are significant life stressors and their negative impact on psychological well-being and quality of life has been thoroughly discussed elsewhere (e.g., Andersen, 1992; Andersen, Kiecolt-Glaser, & Glaser, 1994). Weisman and Worden (1976), for example, noted that the diagnosis of cancer produces an "existential plight," meaning that the news brings shock, disbelief, and emotional turmoil. Sadness, fear, and confusion can characterize the diagnostic period. The majority of people diagnosed with cancer will not only be distressed but the experience will also result in some degree of depressive symptomatology. In fact, 50% of patients will meet the American Psychiatric Association's criteria for psychiatric diagnosis, with the most common being adjustment disorder (Derogatis et al., 1983). Breast cancer alone (one of the most commonly diagnosed cancers in women with over 175,000 new cases yearly in the United States; Landis, Murray, Bolden, & Wingo, 1999), annually yields a subset of women numbering close to 90,000 who may be at risk for clinically significant depressive symptoms due to their cancer experience.

In addition to distress, other variables also may contribute to higher rates of depressive symptoms in the context of cancer, such as sociodemographic, disease, or personality characteristics. Again, we consider the case of breast cancer. Sociodemographic variables (e.g., age, race, SES) are correlated with breast cancer incidence and/or mortality (Faggiano, Partanen, Kogevinas, & Boffetta, 1997; Landis et al., 1999; Schrijvers & Mackenback, 1994), but their relationship to depressive symptoms is inconclusive (Carver et al., 1994; Dean, 1987; Hughson, Cooper, McArdle, & Smith, 1988; Lee et al. 1992; Levy et al., 1992; Pinder et al., 1993; Stanton & Snider, 1993). Disease variables such as stage of disease, type of surgical treatment, and time

since diagnosis/treatment are related, in general, to psychological outcomes in women with breast cancer. In particular, data suggest that women with more advanced disease may have more severe depressive symptoms (e.g., Glanz & Lerman, 1992; Pinder et al., 1993; Stanton & Snider, 1993). Personality variables, most commonly neuroticism, have also been examined. While positive associations between neuroticism and negative affective states (e.g., depressive symptoms) have been found in heterogeneous cancer groups (Jenkins, May, & Hughes, 1991; VanderZee, Buunk, & Sanderman, 1996), the specificity with regards to breast cancer patients needs to be investigated. This potential relationship may be particularly important as neuroticism is consistently associated with psychological distress in other non-cancer populations (e.g., Clark, Watson, & Minneka, 1994; Watson, 1988), and has been proposed as a risk factor for psychological distress (Clark et al., 1994; Watson & Pennebaker, 1989).

Aim of the research

The present study tests the relative explanatory power of measures of objective stressors and subjective stress in the prediction of depressive symptoms. We test this question in an important and naturally occurring paradigm - cancer diagnois and treatment. We choose women recently diagnosed and surgically treated for breast cancer due to the psychologic and biologic distress associated with this stressor (Andersen et al., 1998). Depressive symptoms were the predicted outcome because of its prevalence in this population (van't Spiker et al., 1997). The relationship of objective stressors and subjective stress to depressive symptoms is examined after variables associated with depressive symptoms - sociodemographics, disease characteristics, and the personality trait, neuroticism, were controlled. Even though these variables may be important for further study, they were not the focus of the present study. And so, we controlled for these variables because of their potential confouding relationship with depressive symptoms.

We tested two hypotheses. First, we anticipated that subjective measures of stress would be better predictors of depressive symptoms than objective measures. To enhance the rigor of this comparison we selected high frequency objective stressors important to a woman with breast cancer (e.g., divorce, financial difficulty). Second, globally measured stress was predicted to have a stronger relationship with depressive symptoms than was the stress associated with specific events, namely life event stress and cancer stress. In summary, we explore the relationship among "stress" measures in predicting depressive symptoms for a common, real-life stressor.

Method

Participants

Women newly diagnosed and treated for regional breast cancer were studied (N = 166). Participants were from a larger prospective, longitudinal study (The Stress and Immunity Breast Cancer Project).[1] See Table 2 for sociodemographic and cancer-specific disease characteristics of the sample.

Procedures

Participants were accrued from mid-1994 to mid-1998. The women were recruited primarily from physician's offices at a National Cancer Institute-designated university-affiliated Comprehensive Cancer Center (84%, n = 139). Other participants were self referrals from newspaper advertisements, press releases, and project flyers (16%; n = 27). At the time of assessment, all participants had been surgically treated (lumpectomy or mastectomy) within the preceding 3 months but had not yet begun adjuvant treatment (e.g., chemotherapy, radiation). Psychological, behavioral, and medical/treatment information were collected with an interview and other data collection conducted at the University's General Clinical Research Center or the breast cancer clinic. Disease and surgery information were verified using information from the

women's medical charts/reports and confirmed with primary care providers. All women were paid $20.00 for their participation.

Measures

Control variables

Sociodemographics, disease variables, and personality. Three classes of variables were controlled. The sociodemographic variables included: age, race (White vs. minority status), partner status (yes vs. no), education (years), and family income (dollars per year). The disease variables examined were stage of disease (stage II vs. stage III), extent of surgery (lumpectomy vs. mastectomy), and time since surgery (in days). The personality variable was assessed with the neuroticism factor from Goldberg's Big-Five Factor Measure (1992). Items from this factor were extracted from a factor analysis with the present sample as suggested by Goldberg (personal communication, 1996). Confirming the items as originally provided (Goldberg, 1992), the factor included 16 trait adjectives, 9 positive for the trait of neuroticism (e.g., irritable, nervous) and 7 negative (e.g., even-tempered, at-ease). Each woman rated the extent to which these trait adjectives described her, as compared to others of the same sex and age, on a nine-point Likert scale from "extremely inaccurate" to "extremely accurate." Total scores range from -63.0 to 81.0, with higher scores indicating stronger trait neuroticism. For the present study, the average neuroticism score of the participants was 4.3 (SD = 17; range -32 to 46) and coefficient alpha reliability was .91.

Predictor variables

Objective stressors (life events) and life event stress. The event scale used was adapted from that in the Women's Health Initiative study (Matthews et al., 1997). Participants were asked to indicate if they had experienced any of five stressful life events, ones identified as being

stressful for women (see Table 3). By assessing the occurrence of life events over the previous year, the chronic or long-term impact of life events on later adjustment is assessed. If an event occurred, women then rated how emotionally upsetting the event was (e.g., 3=very much, 2=moderately, 1=not much). Three scores were calculated: presence versus absence of each event (0=not occurred, 1=occurred), the total number of events reported (range 0-5), and the sum of the distress ratings (total range for 5 events, 0-15).

Subjective cancer stress. The IES (Horowitz et al., 1979) is a standardized self-report measure used to examine cognitions involving the re-experiencing (intrusion) and denial of thoughts and avoidant behaviors (avoidance) related to trauma (Miller, 1996). Fifteen items are used, seven for the intrusive subscale (e.g., "I had trouble falling or staying asleep because pictures or thoughts about cancer or having cancer treatment came into my mind") and eight items for the avoidant subscale (e.g., "I tried not to think about it"). Consistent with previous research, the word "event" was changed to "cancer." Women rated each item as experienced in the previous week, using a 4-point Likert scale (not at all=0, rarely=1, sometimes=3, and often=5). Three scores are obtained from the IES, a total score (IES-T) and intrusion (IES-I) and avoidance (IES-A) subscale scores. Total scores can range from 0 to 75 with higher scores indicating increased severity of cancer-related stress. In the present sample the coefficient alpha reliability was .87, consistent with other studies reporting reliabilities of .78-.83 (Cordova et al. 1995, Horowitz et al., 1979; Schwartz et al., 1995).

Subjective global stress. The PSS (Cohen et al., 1983), a measure of perceived stress, is a standardized self-report questionnaire used to determine the extent to which a person judges her/his life to be unpredictable, uncontrollable, and overloading (Cohen et al., 1983). Based on Cohen and Williamson's (1986) recommendation, the ten item PSS-10 was used for its improved

internal reliability and factor structure over other versions of the PSS. Examples of the questions include: "How often have you felt nervous or stressed" and "How often have you felt confident about your ability to handle your personal problems." Women rated how often they experienced the above feelings in the past month on a 5-point Likert scale (from never=1 to very often=5). Total scores range from 0 to 40 and higher scores indicate greater overall stress. Coefficient alpha reliability was .86 in the present sample and ranges from .75 to .86 in the literature (Cohen et al., 1983; Hewitt et al., 1992; Martin et al., 1995; & Pbert et al., 1992).

Outcome variable

Depressive symptoms. The short form (IOWA version, Kohout, Berkman, Evans, & Cornoni-Huntley, 1993) of the Center for Epidemiological Studies Depression scale (CES-D; Comstock & Helsing, 1976; Radloff, 1977) is a standardized self-report questionnaire used to identify current symptoms of depression, with emphasis on depressed affect. The CES-D short form consists of 11 items (e.g., "I felt everything I did was an effort" and "I felt sad") rated on a 3-point Likert scale from "hardly ever or never=0" to "much or most of the time=2." Participants were asked to respond based on their feelings during the previous week. Total scores range from 0 to 22 with higher scores reflecting greater depressive symptoms. Unlike other measures of depressive symptoms (e.g., Beck Depression Inventory, Hamilton Rating Scale for Depression), the CES-D is relatively unaffected by physical symptoms and is, therefore, commonly used in research with medical patients (Devins et al., 1988). Coefficient alpha reliability in the present sample was .74, consistent with other research (Himmelfarb & Murell, 1983; Kohout et al., 1993).

Analytic approach

Correlations among the stress measures (objective stressors, event specific and global

subjective measures) were examined to confirm convergent and discriminative validity. Pearson bivariate correlations were calculated among continuous variables and Spearman rank-order correlations were calculated when one variable was categorical and the other was continuous. Correlations were also used to test the significance and direction of association between the control variables, stress measures, and depressive symptoms. Next, hierarchical multiple regression (HMR) analyses along with squared semi-partials examined the explanatory power of the control variables and stress measures in relation to depressive symptomatology. Variables significantly correlated with depressive symptoms were tested in the regression analyses. Variable entry was determined by the a priori theoretical and empirical rationale specified above.

Results

Preliminary analyses

Descriptive data

Predictor variables. Descriptive data for the objective stressors is provided in Table 4. The majority (74%) of participants experienced at least one life event. The modal subjective stress associated with that event was 3.0=very much upsetting. The most common event reported was the death or serious illness of a relative or close friend. The mean of the IES-T was 25.3 (SD = 14.2, range 0-65), a value at least ½ SD higher than those reported in other breast cancer samples (M = 16.4, Cordova et al., 1995; M = 11.5, Baider, Peretz, & De-Nour, 1992). According to the scale authors, total scores above 19 are considered clinically significant in that feelings/behaviors are at a problematic level (Horowitz, Field, & Classen, 1993). Avoidance and Intrusion subscale means were 12.3 (SD = 7.9, range 0-36) and 12.9 (SD = 8.4, range 0-35), respectively. The average PSS-10 score was 18.6 (SD = 6.8, range 1-36), a value nearing 1 SD higher than the mean score from a national probability sample of adults (M = 13.02; Cohen and

Williamson, 1986). In summary, the data suggest that the participants were reporting significant psychological stress across both objective and subjective measures.

Outcome variable. CES-D scores ranged from 0 to 14 ($M = 6.1$; $SD = 3.5$). Based on previous psychometric studies of the CES-D (Andresen, Malgren, Carter, & Patrick, 1994), a cut-off score of ≥ 10 was considered suggestive of clinical depression. This score was also 1 SD above the sample mean. As can be seen in Figure 1, 19% ($n = 32$) of the participants had CES-D scores meeting/exceeding the cut-off. An additional 9% ($n = 15$) of the women had the score of 9, one point below the cut-off score. In all, one fifth of the women were experiencing depressive symptoms of possible clinical importance (i.e., ≥ 10). This is comparable to rates of depressive symptoms found in previous studies of women with breast cancer (Rijken, deKruif, Komproe, & Roussell, 1995; Watson et al., 1990).

Convergent and discriminative validity among the stress measures

Correlations between objective stressors and subjective stress measures are presented in Table 5 and demonstrate expected convergent and discriminant validity relationships. As would be predicted, number of events and perceived stress associated with those life events were correlated (17 of 21 correlations were significant ranging from .15 to .91). Importantly, there were zero or smaller correlations between these life events and the IES-T and its subscales (only 4 of 21 correlations were significant and they ranged from .13 to .21), suggesting that the objective life event measures and the subjective cancer stress measures were assessing differing aspects of stress. This pattern of correlations is also consistent with the findings of other research (e.g., Cohen et al., 1983; Pbert et al., 1992). In regards to the subjective cancer stress measure (IES), the data show that the subscales of the measure are correlated ($r = .54$), non-overlapping, and consistent with previous research reporting correlations of .51 (Epping-Jordan, Compas, &

Howell, 1994) and .68 (Cordova et al., 1995). The subjective measure of global stress (PSS-10) was related to most of the other stress measures (9 of 10 correlations were significant ranging from .13 to .51), though again, non-overlapping. Furthermore, correlations within measures (e.g., subscales of the IES) were higher than correlations between measures (e.g., IES and PSS-10). Finally, the magnitude of the correlations among the subjective stress measures was greater than those with objective stressors (e.g., Cohen et al., 1983).

Primary analyses

Correlations

Of the nine control variables tested (age, race, partner status, education, income, stage of disease, type of surgery, DSS, and neuroticism), only two were significantly correlated with depressive symptoms, race ($r = -.19$, $p < .01$) and neuroticism ($r = .38$, $p < .0001$). Thus, both being of minority status (i.e., African American or Hispanic) and having higher levels of neuroticism were related to higher CES-D scores. Based on these results, race and neuroticism were included in the regression analyses.

Correlations among objective stressors, subjective stress measures, and depressive symptoms are presented in Table 6. The total number of life events and life event stress, while significantly correlated with depressive symptoms, were not included in further analyses due to multicollinearity with absence/presence of objective stressors.[2] As "major financial difficulty" and "major conflict with children or grandchildren" were the life events significantly ($p < .05$) correlated with CES-D scores, they were also included. As expected, the subjective measures (life event stress, IES-T and its subscales, and PSS-10) were significantly correlated with CES-D scores ($p < .01$). As the shared variance between the PSS-10 and the CES-D was noteworthy ($r = .63$; 40%), we wished to rule out the possiblity of measure overlap at the item level. Results

of a factor analysis verified no overlap of items between measures.[3] Thus, the results described below are not confounded by shared item/content variance between the PSS-10 and CES-D.

Regression

HMR was used to examine the relative power of objective stressors, event specific subjective stress, and subjective global stress in predicting depressive symptoms after controlling for the effects of race and neuroticism. The a priori entry was as follows: Step 1) race, 2) neuroticism, 3) objective stressors (major conflict with children or grandchildren and major financial difficulty), 4) IES-T, and 5) PSS-10.

Table 7 provides the results of the HMR, emphasizing the change in variance in depressive symptoms accounted for when the control variables (race and neuroticism) and the predictors (major financial difficulty, major conflict with children or grandchildren, IES-T, and PSS-10) were added to the model. With HMR, 51% (total adjusted $R^2 = .496$) of the variance in depressive symptoms was accounted for by the full model. Of note, global stress remained a significant predictor of depressive symptoms after accounting for the effect of all the other variables in the regression.

Table 8 shows results for the final regression model, equivalent to the full model represented by Step 5 in Table 7. In this model, squared semi-partial correlations, sr^2, indicate the amount of variance accounted for by a given variable above and beyond all other variables in the regression model (Cohen & Cohen, 1983). Therefore, based on the sr^2 for the final regression model, which indicates the amount of variance accounted for by each variable had it been last in the regression equation, the best predictor of depressive symptoms was global stress (10%), followed closely by cancer stress (8%). Race, the remaining significant variable in the final regression model, added little unique variance (approximately 1%) in predicting depressive

symptoms.

While neuroticism and the objective stressors (major financial difficulty and major conflict with children or grandchildren), introduced at Steps 2 and 3 respectively, added significant amounts of variance in the HMR, neither were significant predictors of depressive symptoms in the final regression model. Neuroticism may not have been signficant due to global stress mediating its influence or to multicollinearity (neuroticism was most highly correlated with global stress, $r = .45$, $p < .0001$, as opposed to any other variable in the study). However, the objective stressors did approach significance ($p. = .057$). In examining the squared semi-partials (sr^2) for these variables, the unique variance accounted for in depressive symptoms is mostly attributable to the contribution of major financial difficulty (approximately 1%) rather than to that of major conflict with children or grandchildren (0%).

Follow-up analyses

Because of the empirical and clinical importance of the cancer stress measure, we wished to test the relative contribution of avoidance versus intrusive thoughts/behaviors to depressive symptoms. Therefore, a second regression was conducted using the IES subscales, IES-A and IES-I, in place of the IES-T. Variables were entered as before: Step 1) race, 2) neuroticism, 3) major conflict with children or grandchildren and major financial difficulty, 4) IES-A, 5) IES-I, and 6) PSS-10. IES-A was entered before IES-I because of its weaker relationship with psychological outcomes. Results from this follow-up indicate that, 52% (total adjusted $R^2 = .500$) of the variance in depressive symptoms was accounted for by the HMR, $F(7, 158) = 24.54$, $p < .0001$. Specifically, the IES-A did not contribute a significant increment of unique variance to the final model (beta = .089, $t(160) = 1.31$; $sr^2 = .005$). This finding is consistent with previous literature (e.g., Baider & De-Nour, 1997; Cordova et al., 1995), zero or weak relationships

between avoidant thoughts/behaviors and psychological distress. However, both intrusive thoughts/behaviors (IES-I) and global stress (PSS-10) were predictive of depressive symptoms in the final regression model (IES-I: beta = .291, $t(159) = 4.01$, $p < .0001$ and PSS-10: beta = .379, $t(158) = 5.32$, $p < .0001$) accounting for 5% ($sr^2 = .049$) and 9% ($sr^2 = .086$) of the variance, respectively. Again, global stress was the best predictor of depressive symptoms.

Discussion

The present study examined the relative explanatory power of objective stressors (life events) and subjective stress measures (event specific, global) in relationship to depressive symptoms. This examination occurred in the context of an important, naturally occurring event, the diagnosis and treatment of cancer. Our hypotheses were confirmed: 1) subjective measures of stress were better predictors of depressive symptoms than an objective measure (life events); and 2) a measure of one's global perceptions of stress was a better predictor of depressive symptoms than a measure of perceived stress for the specific event (i.e., cancer).

These findings are consistent with others (e.g., Cohen et al., 1983) and underscore the importance of perceptions or appraisals of stress (instead of or in addition to the assessment of events, per se) when examining the relationship between stress and psychological outcomes. Indeed, a global perception of stress, as assessed with the PSS-10, was the strongest predictor of depressive symptoms. While the difference between the contribution of the PSS-10 and the event specific subjective measure (IES) was small (10% vs. 8%, respectively), this finding remains impressive considering the clinical importance of the event -- cancer diagnosis and treatment. Interestingly, many women in the study have told us that they were approached for study participation on "the worst days of my life." Relatedly, one of the most common reasons for refusing participation was the report of feeling "too stressed" to participate. Furthermore, when

the mean values on the PSS-10 and IES were compared with data from other cancer or normative samples, the present values were, at a minimum, one-half to one standard deviation higher. This provides empirical support for the fact that many of the women were stressed not only by their cancer experience but with life, in general, as well.

In comparison to the perceptions of global stress and stress specific with the cancer "event," the contribution of other recent, difficult, and upsetting events -- such as death or serious illness of a close friend or relative or major financial difficulty-- to the prediction of depressive symptoms was minimal. The contribution of these other stressful events may be smaller because their impact may have lessened with time. For instance, these events occurred at some point in the past 12 months, and they may have resolved by the time of assessment. Meanwhile, the time from cancer diagnosis to post surgery recovery and study participation was, on average, a matter of 4 weeks. The confounding of the rating interval with the measure (e.g., past 12 months for the objective stressors vs. past month for global stress and past week for cancer specific stress) has a statistical effect on the magnitude of the correlation between the measures and the outcome. In this case, the relationship between the subjective stress measures and the outcome would be expected to be higher because of the shorter and more proximal rating interval. Another methodological difference between the measures is the item format. That is, measures assessing the degree of distress associated with life events typically use only one item per event, which reduces the reliability of the measure. This contrasts with the multiple item format of a measure like the IES. Taken together, these methodologic aspects of objective stress measures may contribute to the findings reported here, as well as others, which suggest that event measures are, on average, weaker predictors in comparison to subjective global stress measures (Cohen et al., 1983; Martin et al., 1995; Pbert et al., 1992), even when some of the objective events rated

are the most difficult ones individual's can experience (e.g., death of a loved one).

Finally, in testing the relationship between stress and depressive symptoms, we controlled for variables such as sociodemographics (age, race, partner status, education, and income) and personality (neuroticism), all of which are known to covary with stress or the perception of stress. While important for study in their own right, these variables were controlled here because they were not the focus of study. In addition to personality and sociodemographic variables, we also chose ones relevant for the present paradigm--disease characteristics (e..g, stage of disease, surgery type, days since surgery). Of all the control variables, only a sociodemographic one, minority status, was significantly related to depressive symptoms in the final model of the HMR. This finding does not reflect an SES difference in the sample, as we separately tested and found no significant differences in family income, years of education, and partner status. It is possible that this finding is related to other variables associated with race/ethnicity and cancer outcomes such as knowledge and attitudes and/or access to adequate care (see Meyerowitz, Richardson, Hudson, & Leedham, 1998, for a review). As the number of minority participants in the present study was small ($\underline{n}$ = 16, 10% of the total sample), the latter finding will require replication before a general conclusion can be made. In any case, the inclusion of the control variables provided data to rule out alternative, plausible hypotheses for our findings.

Clinical implications of the findings

In addition to the methodologic focus of this study, the findings also provide an important look at the emotional crisis that surrounds cancer diagnosis and surgery. Our earlier research on the emotional responses to cancer diagnosis (Andersen et al., 1989) found that depressive and confused moods were unique emotional responses. While anxious reactions were common as well, they are likely part of the general emotional response to a medical diagnosis and the

anticipation of medical treatment, rather than cancer, per se. More recently, we have reported that cancer specific stress (as indexed by the IES) is not only emotionally upsetting, but is related to a negative biologic response -- immune down regulation (Andersen et al., 1998), and we have hypothesized that such a scenario may adversely impact the course of the disease (Andersen et al., 1994). These data indicate that the stress indexed by the IES, coupled with the global feelings of stress and recent life event stressors, may conspire to heighten one's risk for depressive symptomatology. In reviewing the literature on psychosocial interventions (Andersen, 1992), we noted that stress reduction is a component of successful interventions. Considering these data along with our other studies, they suggest that stress reduction should be included to not only lower stress and anxiety, but to possibly reduce other negative affective symptoms (e.g., depressive ones) which can also have important biologic effects (Herbert & Cohen, 1993).

In considering other specific findings and their clinical importance, while a majority of women reported experiencing the death or serious illness of a close friend or relative in the previous 12 months (a fact not surprising considering the age range of the sample), it was "major financial difficulty" and "major conflict with children or grandchilden" that were significantly correlated with depressive symptoms ($p <$ of .01 and .05, respectively), and these events approached significance in the HMR ($p < .057$) as predictors of depressive symptoms. While we do not know if these life events represented chronic circumstances or new stressors, research has indicated that the cancer experience can have detrimental consequences on both finances (e.g., loss of income due to work absences, increased insurance costs; McKenna, 1991; McKenna & Toghia, 1989) and family relationships (e.g., increased tension between partners with young children in the home, Vess, Moreland, & Schwebel, 1985; decreased availability of support due to increased family/partner strain/distress, Baider & De-Nour, 1988; Cassileth et al., 1985; see Sales,

Schulz, & Biegel, 1992, for a review). As 28% of all households are headed by unmarried women and 57% of all women work outside the home (U.S. Bureau of the Census, 1995; 1996), these two stressors, in particular, may be important to the psychological functioning of women with breast cancer.

One can easily forsee how financial and/or family problems could effect multiple aspects of the cancer experience. For instance, these stressors may be involved in the selection of medical therapies (e.g., insurance coverage of chemotherapy vs. bone marrow transplantation) and/or delay of medical treatment (work and/or child care conflicts), create transportation difficulties (multiple family obligations), impair the quality/availability of support (e.g, increased tension in the home) , and decrease, overall, quality of life. Therefore, the data suggest that these stressors (whether new or old) and their potential negative impact on the already stressful experience of a cancer diagnosis may increase one's vulnerability to depressive symptoms, affect treatment compliance, and possibly longterm survival as well (especially if women are not receiving recommended medical treatment; e.g., Bonadonna & Valagussa, 1981; Coates et al., 1992). Health care providers may want to be particularly aware of those women who are struggling financially and/or experiencing interpersonal conflicts. Linking women with appropriate psychological, social, and/or financial services would be important. In particular, the benefits of psychological interventions (e.g., improved coping, better communication, increased mood) for people with cancer have been well-documented (Andersen, 1992).

In conclusion, these data demonstrate the value of assessing both objective stressors and subjective stress (event specific and global). Such information can increase our understanding of how life events and stress perceptions are related to psychological functioning as well as identify circumstances in which people may be in need of intervention. Given the design of the current

study, no causal inferences can be made. However, future research can examine the reliability of these relationships longitudinally, establish causal explanations, and test their generalizability with other cancer groups.

References

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC.

Andersen, B.L. (1992). Psychological interventions for cancer patients to enhance quality of life. Journal of Consulting and Clinical Psychology, 60, 552-568.

Andersen, B. L., Anderson, B., & deProsse, C. (1989). Controlled prospective longitudinal study of women with cancer: II. Psychological outcomes. Journal of Consulting and Clinical Psychology, 57, 692-697.

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses after surgical treatment for regional breast cancer. Journal of the National Cancer Institute, 90, 30-36.

Andersen, B. L., Kiecolt-Glaser, J. K., & Glaser, R. (1994). A biobehavioral model of cancer stress and disease course. American Psychologist, 49, 389-404.

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for depression in well older adults: Evaluation of a short form of the CES-D. American Journal of Preventive Medicine, 10(2), 77-84.

Andrykowski, M. A., Cordova, M. J., Miller, T. W., & Studts, J. L. (1998). Posttraumatic stress disorder after treatment for breast cancer: Prevalence of diagnosis and use of the PTSD checklist (PCL-C) as a screening instrument. Journal of Consulting and Clinical Psychology, 66, 001-005.

Baider, L., & De-Nour, A.K. (1988). Adjustment to cancer: Who is the patient - the husband of the wife? Israil Journal of Medicine Sciences, 24, 631-636.

Baider, L., & De-Nour, A. K. (1997). Psychological distress and intrusive thoughts in cancer

patients. Journal of Nervous and Mental Disease, 185(5), 346-348.

Baider, L., Peretz, T., & De-Nour, A. K. (1992). Effect of the Holocaust on coping with cancer. Social Science & Medicine, 34(1), 11-15.

Baum, A., Gatchel, R. J., Schaeffer, M. A. (1983). Emotional, behavioral, and physiological effects of chronic stress at Three Mile Island. Journal of Consulting & Clinical Psychology, 51(4), 565-572.

Bebbington, P., Wilkins, S., Jones, P. B., & Forester, A., et al. (1993). Life events and psychosis: Initial results from the Camberwell Collaborative Psychosis Study. British Journal of Psychiatry, 162, 72-79.

Bonadonna, G., & Valagussa, P. (1981). Dose-response effect of adjuvant chemotherapy in breast cancer. New England Journal of Medicine, 43, 169.

Browne, M.W. (1972). Oblique rotation to a partially specified target. British Journal of Mathematical and Statistical Psychology, 25, 207-212.

Browne, M.W., Cudeck, R., Tateneni, K., & Mels, G. (1998). CEFA: Comprehensive Exploratory Factor Analysis. WWW document and computer program. URL http://quantrm2.psy.ohio-state.edu/browne/

Bukberg, J., Penman, D., & Holland, J.C. (1984). Depression in hopitalized cancer patients. Psychosomatic Medicine, 46(3), 199-212.

Bull, B. A., & Drotar, D. (1991). Coping with cancer in remission: Stressors and strategies reported by children and adolescents. Journal of Pediatric Psychology, 16(6), 767-782.

Carver, C. S., Pozo-Kaderman, C., Harris, S. D., Noriega, V., Sheier, M. F., Robinson, D. S. Ketcham, A. S., Moffat, F. L. Jr., & Clark, K. C. (1994). Optimism versus pessimism predicts the quality of women's adjustment to early stage breast cancer. Cancer, 73(4),

1213-1220.

Cassileth, B., Lunk, E., Strouse, T., Miller, D., Brown, L, & Cross, P. (1985). A psychological analysis of cancer patients and atheir next-of-kin. Cancer, 55, 72-76.

Clark, L. A., Watson, D., & Minneka, S. (1994). Temperament, personality, and the mood and anxiety disorders. Journal of Abnormal Psychology, 103, 103-116.

Coates, R.J., Bransfield, D.D., Wesley, M., Hankey, B., Eley, J.W., Greenberg, R.S., et al. (1992). Differences between black and white women with breast caner in time from symptoms recognition to medical consultation. Journal of the National Cancer Institute, 84, 938-950.

Cobb, S., & Kasl, S. V. (1977). Termination: The Consequences of Job Loss. Report No. 76-1261. Cincinnati, OH: National Institute for Occupational Safety and Health, Behavioral and Motivational Factors Research.

Cohen, J. & Cohen, P. (1983). Applied Multiple Regression/Correlation for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. Journal of Health and Social Behavior, 24, 385-396.

Cohen, S., & Williamson, G. M. (1986). Perceived stress in a probability sample of the United States. In S. Spacapan & S. Oskamp (Eds.), The Social Psychology of Health , (pp. 31-67), Newbury Park, CA: Sage.

Comstock, G. W., & Helsing, K. J. (1976). Symptoms of depression in two communities. Psychological Medicine, 6, 551-563.

Cooper, C.L., & Faragher, E.B. (1993). Psychosocial stress and breast cancer: The inter-relationship between stress events, coping strategies and personalities. Psychological

Medicine, 23(3), 653-662.

Cordova, M. J., Andrykowski, M. A., Kenady, D. E., McGrath, P. C., Sloan, D. A., & Redd, W. H. (1995). Frequency and correlates of posttraumatic-stress-disorder-like symptoms after treatment for breast cancer. Journal of Consulting and Clinical Psychology, 63(6), 981-986.

Dean, C. (1987). Psychiatric morbidity following mastectomy: Preoperative predictors and types of illnesses. Journal of Psychosomatic Research, 31(3), 385-392.

Derogatis, L. R., Morrow, G. R., Fetting, J., Penman, D., Piasetsky, S., Schmale, A. M., Henrichs, M., & Carnicke, C. L. (1983). The prevalence of psychiatric disorders among cancer patients. Journal of the American Medical Association, 249, 751-757.

Devins, G. M., Orme, C. M., Costello, C. G., Binik, Y. M., Frizzell, B., Stam, H. J., Pullin, W. M., (1988). Measuring depressive symptoms in illness populations: Psychometric properties of the Center for Epidemiologic Studies Depression (CES-D) Scale. Psychological Health, 2, 139-156.

Dohrenwend, B. S., & Dohrenwend, B. P. (1974). Overview and prospects for research on stressful life events. In B. S. Dohrenwend & B. P. Dohrenwend (Eds.), Stressful life events: Their nature and effects (pp. 313-331). New York: Wiley.

Dohrenwend, B. S., & Dohrenwend, B. P. (1978). Some issues in research on stressful life events. Journal of Nervous and Mental Disease, 166, 7-15.

Epping-Jordan, J. E., Compas, B. E., Howell, D. C. (1994). Predictors of cancer progression in young adult ment and women: Avoidance, intrusive thoughts, and psychological symptoms. Health Psychology, 13(6), 539-547.

Faggiano, F., Partanen, T., Kogevinas, M., Boffetta, P. (1997). Socioeconomic differences in

cancer incidence and mortality. IARC Scientific Publications, (138), 65-176.

Finlay-Jones, R., & Brown, G. W. (1981). Types of stressful life events and the onset of anxiety and depressive disorders. Psychological Medicine, 11(4), 803-815

Ginsberg A., Price, S., Ingram, D., & Nottage E. (1996). Life events and the risk of breast cancer: a case-control study. European Journal of Cancer, 32A(12), 2049-2052.

Glanz, K., & Lerman, C. (1992). Psychosocial impact of breast cancer: A critical review. Annals of Behavioral Medicine, 14(3), 204-212.

Goldberg, L.R. (1992). The development of markers for the Big-Five factor structure. Psychological Assessment, 4(1), 26-42.

Grassi, L. Malacarne, P., Maestri, A., & Ramelli, E. (1997). Depression, psychosocial variables and occurrence of life events among patient with cancer. Journal of Affective Disorders, 44(1), 21-30.

Hall, M., & Baum, A. (1995). Intrusive thoughts as determinants of distress in parents of children with cancer. Special Issue: Rumination and intrusive thoughts. Journal of Applied Social Psychology, 25(14), 1215-1230.

Herbert, T.B., & Cohen, S. (1993). Depression and immunity: A meta-analytic review. Psychological Bulletin, 113, 472-486.

Hewitt, P. L., Flett, G. L., & Mosher, S. W. (1992). The perceived stress scale: Factor structure and relation to depression symptoms in a psychiatric sample. Journal of Psychopathology and Behavioral Assessment, 14(3), 247-257.

Hills, H., & Norvell, M. (1991). An examination of hardiness and neuroticism as potential moderators of stress outcomes. Behavioral Medicine (pp. 31-38). Washington D.C.: Heldref Publications.

Himmelfarb, S., & Murell, S. A. (1983). Reliability and validity of five mental health scales in older persons. Journal of Gerontology, 38, 333-339.

Holmes, T. H., & Rahe, R. H. (1967). The social readjustment rating scale. Journal of Psychosomatic Research, 11, 213-218.

Horesh, N., Apter, A., Lepkifker, E., & Ratzoni, G., et al. (1995). Life events and severe anorexia nervosa in adolescence. Acta Psychiatrica Scandinavica, 91(1), 5-9.

Horowitz, M., Wilner, N., Alvarez, W. (1979). Impact of event scale: a measure of subjective stress. Psychosomatic Medicine, 41(3), 209-218.

Horowitz, M., Field, N., & Classen, C. (1993). Stress response syndromes and their treatment. In L. Goldberger, S. Breznitz, et al., (Eds.). Handbook of stress: Theoretical and clinical aspects (2nd ed.). NY: Free Press.

Hughson, A. V., Cooper, A. F., McArdle, C. S., & Smith, D. C. (1988). Psychosocial consequences of mastectomy: Levels of morbidity and associated factors. Journal of Psychosomatic Research, 32(4-5), 383-391.

Jenkins, P. L., May, V. E., Hughes, L. E. (1991). Psychological morbidity associated with local recurrence of breast cancer. International Journal of Psychiatry in Medicine, 21(2), 149-155.

Kuiper, N. A., Olinger, L.J., & Lyons, L.M. (1986). Global perceived stress level as a moderator of the relationship between negative life events and depression. Journal of Human Stess, 12(4), 149-153.

Kohout, F. J., Berkman, L. F., Evans, D. A., & Cornoni-Huntley, J. (1993). Two shorter forms of the CES-D depression symptoms index. Journal of Aging and Health, 5, 179-193.

Landis, S.H., Murray, T., Bolden, S., & Wingo, P.A. (1999). Cancer statistics, 1999. CA-A:

Cancer Journal for Clinicians, 49, 8-31.

Lazarus, R. S., & Folkman, S. (1984). Stress, Coping, and Adaptation. NY: Springer.

Lee, M. S. Love, S. B., Mitchell, J. B., Parker, E. M., Reubens, R. D., Watson, J. P., Fentiman, I. S., & Hayward, J. L. (1992). Mastectomy or conservation for early breast cancer: psychological morbidity. European Journal of Cancer, 28A(8-9), 1340-1344.

Levy, S. M., Haynes, L. T., Herberman, R. B., Lee, J., McFeeley, S., & Kirkwood, J. (1992). Mastectomy versus breast conservation surgery: Mental health effects at long-term follow-up. Health Psychology, 11(6), 349-354.

Matthews, K.A., Shumaker, S.A., Bowen, D.J., Langer, R.D., Hunt, J.R., Kaplan, R.M., Klesges, R.C., Ritenbaugh, C. (1997). Women's health initiative: Why now? What is it? What's new? American Psychologist, 52(2), 101-116.

Manfro, G. G., Otto, M.W., McArdle, E. T., & Worthington, J. J. III, et al. (1996). Relationship of antecedent stressful life events to childhood and family history of anxiety and the course of panic disorder. Journal of Affective Disorders, 41(2), 135-139.

Martin, R. A., Kazarian, S. S., & Breiter, H. J. (1995). Perceived stress, life events, dysfunctional attitudes, and depression in adolescent psychiatric patients. Journal of Psychopathology and Behavioral Assessment, 17(1), 81-95.

McKenna, R. (1991). Supportive care and rehabilitation of the cancer patient. In A. Holleb, D. Fink, and Murphy, G. (Eds). Clinical Oncology. Atlanta, GA: American Cancer Society.

McKenna, R., & Toghia, N. (1989). Maximizing the productive activities of the cancer patient: Policy issues in work and illness. In I.Borofsky (Ed), The cancer patient. New York: Praeger.

Meyerowitz, B., Richardson, J., Hudson, S., & Leedham, B. (1998). Ethnicity and cancer

outcomes: Behavioral and psychosocial considerations. Psychological Bulletin, 123(1), 47-70.

Miller, T. W. (1996). Current measures in the assessment of stressful life events. In T.W. Miller (Ed.), Theory and assessment of stressful life events. (pp. 209-233). Madison, CT: International Universities Press.

Pbert, L., Doerfler, L. A., & DeCosimo, D. (1992). An evaluation of the perceived stress scale in two clinical populations. Journal of Psychopathology and Behavioral Assessment, 14(4), 363-375.

Pinder, K. L., Ramirez, A. J., Black, M. E., Richardson, M. A., Gregory, W. M., & Rubins, I. D. (1993). Psychiatric disorder with patients with advanced breast cancer: Prevalence and associated factors. European Journal of Cancer, 29, 524-527.

Radloff, L.S. (1997). The CES-D scale: A self-report depression scale for research in the general population. , Applied Psychological Measurement, 1, 385-401.

Ramirez, A. J., Craig, T. K., Watson, J. P., Fentiman, I. S., North, W. R., Rubens, R. D. (1989). Stress and relapse of breast cancer. British Medical Journal,298(6669), 291-3.

Rijken, M., deKruif, A., Komproe, I. H., & Roussell, J. (1995). Depressive symptomatology of post-menopausal breast cancer patients: A comparison of women recently treated by mastectomy or breast conserving therapy. European Journal of Surgical Oncology, 21, 498-503.

Roberts, F. D., Newcomb, P. A., Trentham-Dietz, A., Storer, BE. (1996). Self-reported stress and risk of breast cancer. Cancer, 77(6), 1089-93.

Sales, E., Schulz, R., & Biegel, D. (1992). Predictors of strain in fmailies of cancer patients: A review of the literature. Journal of Psychosocial Oncology, 10, 1-26.

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: Development of the life experiences survey. Journal of Consulting and Clinical Psychology, 46, 932-946.

Schrijvers, C.T., & Machenbach, J.P. (1994). Cancer patient survival by socioeconomic status in seven countries: a review for six common cancer sites. Journal of Epidemiology and Community Health, 48(6) 441-446.

Schulz, R., Williamson, G. M., Knapp, J. E., Bookwala, J., et al. (1995). The psychological, social, and economic impact of illness among patients with recurrent cancer. Journal of Psychosocial Oncology, 13(3), 21-45.

Schwartz, M. D., Lerman, C., Miller, S. M., Daley, M., & Masny, A. (1995). Coping disposition, perceived risk, and psychological distress among women at increased risk for ovarian cancer. Health Psychology, 14(3), 232-235.

Stanton, A. L., & Snider, P. R. (1993). Coping with breast cancer diagnosis: a prospective study. Health Psychology, 12(1), 16-23.

Stroebe, W., Stroebe, M. S., Gergen, K. J., & Gergen, M. (1982). The effects of berevement on mortality: A social psychological analysis. In J. R. Eiser (Ed.), Social Psychology and Behavioral Medicine (pp. 527-561). New York: Wiley.

Tope, D. M., Ahles, T. A., Siberfarb, P. M. (1993). Psycho-oncology: Psychological well-being as one component of quality of life. Psychotherapy & Psychosomatics, 60(3-4), 129-147.

U.S. Bureau of the Census. (July 1995/May 1996). Women in the United States: A Profile. Statistical Brief. Washington, D.C.: U.S. Department of Commerce.

Van Servellen, G., Sarna, L., Padilla, G., Brecht, M.L. (1996). Emotional distress in men with life-threatening illness. International Journal of Nursing Studies, 33(5), 551-65.

van't Spiker, A., Trijsburg, R.W., & Duivenvoorden, H.J. (1997). Psychological sequelae of cancer diagnosis: A meta-analytical review of 58 studies after 1980. Psychosomatic Medicine, 59,3, 280-293.

VanderZee, K. I., Buunk, B. P., Sanderman, R. (1996). The relationship between social comparison processes and personality. Personality & Individual Differences, 20(5), 551-565.

Varni, J. W., Katz, E. R., Colegrove, R., Dolgin, M. (1994). Perceived stress and adjustment of long-term survivors of childhood cancer. Journal of Psychosocial Oncology, 12(3), 1-16.

Vess, J., Moreland, J., & Schwebel, A. (1985). A followup study of role functioning and the psychosocial environment of families of cancer patients. Journal of Psychosocial Oncology, 3, 1-14.

Vinokur, A., & Selzer, M.L. (1975). Desirable versus undesirable life events: Their relationships to stress and mental distress. Journal of Personality and Social Psychology, 32(2), 329-337.

Warheit, G. J. (1979). Life events, coping, stress, and depressive symptomatology. American Journal of Psychiatry, 136(4-B), 502-507.

Watson, D. (1988). Intraindividual and interindividual analyses of positive and negative affect: Their relation to health complaints, perceived stress, and daily activities. Journal of Personality and Social Psychology, 54, 1020-1030.

Watson, D., & Pennebaker, J. W. (1989). Health complaints, stress, and distress: Exploring the central role of negative affectivity. Psychological Review, 96, 234-254.

Watson, M., Greer, S., Rowden, L., Gorman, C., Robertson, B., Bliss, J. M., & Tunmore, R. (1991). Relationships between emotional control, adjustment to cancer and depression

and anxiety in breast cancer patients. Psychological Medicine, 21(1), 51-57.

Weisman, A. D., & Worden, J. W. (1976). The existential plight in cancer: Significance of the first 100 days. International Journal of Psychiatry in Medicine, 7, 1-15.

Author Note

Deanna M. Golden-Kreutz, Department of Psychology; Mary Elizabeth Courtney, Department of Psychology (now at Ohio University, Athens, Ohio); Vicki DiLillo, Department of Psychology (now at the University of Alabama, Birmingham); and Barbara L. Andersen, Department of Psychology.

The Stress and Immunity Breast Cancer Project is an ongoing study conducted at the Department of Psychology in collaboration with the James Cancer Hospital and Research Institute, at The Ohio State University, Columbus, Ohio. The study is supported by grants from the American Cancer Society (PBR-89), the Longaberger Company-American Cancer Society Grant for Breast Cancer Research (PBR-89A), the U.S. Army Medical Research Acquisition Activity Grants (DAMD17-94-J-4165 and DAMD17-96-1-6294), and the National Institutes of Mental Health (1 RO1 MH51487), the General Clinical Research Center (MO1-RR0034), the Ohio State University Comprehensive Cancer Center Core Grant from the National Cancer Institute (P30 CA16058), and the Department of Psychology and the College of Social and Behavioral Sciences at The Ohio State University.

We thank the participants for their assistance. In addition, we thank the following individuals for their contributions: research assistants, Susan Aarestad, Nicole Chaput, Angie Collier, Larisa Demshuk, Melissa Douglas, Sarah Grimes, Katheryn Pingel, Elizabeth Street Bromet, Jessica Walker, Laura Wielonski, and Beth Putz for conducting assessments; surgical oncologists William Farrar, William Burak, William Carson, Julian Kim, Gregory LaValle, Deborah Martinez, Michael Walker, and Lisa Yee and medical oncologists Kelly Cawley, Chris Rhoades, Arthur Sagone, Victoria Seewalt, Michael Stanek, and James Ungerleider for OSU accural; and Drs. Charles Emery and Robert MacCallum for helpful comments on the manuscript.

We would also like to give a special thank you to Georita Frierson and Dr. Michael Browne for their assistance in conducting and interpreting the factor analysis.

Correspondence concerning this article should be addressed to Deanna M. Golden-Kreutz, Department of Psychology, 1885 Neil Avenue Mall, 245 Townshend Hall, The Ohio State University, Columbus, Ohio, 43210-1222. E-mail: golden-kreutz.1@osu.edu. Reprint requests should be sent to Barbara L. Andersen at the above address. E-mail: andersen.1@osu.edu.

Footnotes

[1]Data from the first 116 women accrued to the Stress and Immunity Breast Cancer Project (including 116 of the 166 women included here) have appeared in a report of the negative relationship between stress (as indexed by the IES) and multiple immune indicators (Andersen et al., 1998). Aside from the IES, there is no overlap of measures between Andersen et al. (1998) and the present report.

[2]The correlation between the total number of life events and life event stress was $r = .91$ ($p < .0001$), indicating shared variance. Including both of the variables in the regression equation would have been redundant. Of additional concern was the collinearity between the objective stressors and the perceived stress associated with them. Collinearity was likely due to the strategy of assessing life event stress with one item using a 3-point scale, which did not allow for sufficient variance among participants. We tested this variance using oneway ANOVAS with CES-D as the dependent variable and the 3 life event distress categories (not much, some, very much) as the independent variable for all 5 of the life events assessed. None of the ANOVAS were significant at $p < .05$, all F's ≤ 2.7. Thus, experiencing a life event was akin to being distressed by that event. As all women did not experience a life event, there was greater variation between those women who did not experience a life event versus those women who did experience one or more life events. As such, it was decided to enter only those objective stressors significantly correlated with CES-D scores in the regression equation.

[3]We conducted a PACE factor analysis using the program CEFA (Browne, Cudeck, Tateneni, & Mels, 1998). According to previous research, the short form of the CES-D has 4 factors (1-depressed affect; 2-postitive affect; 3-somatic complaints, and 4-interpersonal problems; Kohout et al., 1993) while the PSS-10 has 2 identified factors (1-distress; 2-coping;

Cohen & Williamson, 1986; Hewitt et al., 1992; Martin et al., 1995). We combined the PSS-10 and CES-D, and oblique rotation to a partially specified target (Browne, 1972) was carried out to test the factor loadings for construct redundancy. Loadings anticipated to be zero were minimized in the rotation process and values of the remaining loadings were left unspecified. Thus a pattern suggested by current research (6 factors) was tested and a rotation to a solution as close to the target as possible was carried out. As an additional check, we also conducted factor analyses for 4, 5, and 7 factors.

The RMSEAs, measuring goodness of fit, for the factor solutions were as follows: 4 factors = .072, 5 factors = .067, 6 factors = .058, and 7 factors = .060. The RMSEA values for the 4 and 5 factor solutions were unsatisfactory (scores $\leq$ .05-.06 are judged acceptable). While the RMSEA values for the 6 and 7 factor solutions were both acceptable, the 7 factor solution showed evidence of overfactoring as indicated by the direct quartamin rotation in which there were two moderate loadings on the seventh factor and the other factor loadings were low, negative values (approximating zero). Therefore, the variance accounted for by the seventh factor was uninterpretable. The 6 factor solution, however, demonstrated high loadings that corresponded to the target and reflected previous findings. Additionally, the confidence intervals corresponding to the target zero loadings generally overlapped with zero and the residuals appeared satisfactory since they did not demonstrate a pattern among the items. These results were not only consistent with previous research but, in fact, indicated no item overlap among the two measures in the present sample.

Table 1

Types of Stress Measures

Objective (stressors)
- Type of Life Event (e.g., finanical loss, bereavement, job loss)
- Total Number of Life Events
Subjective (perceived stress)
- Event Specific (stress associated with identified event)
- Global (stress associated with life in general)

Table 2

Sociodemographic and Disease Characteristics of Sample

	Sociodemographics n (%)
Age (years):	M(SD) = 50(11)
Race: White	150 (90)
Minority	16 (10)
African American	14 (9)
Hispanic	2 (1)
Living with spouse/partner: Yes	119 (72)
No	47 (28)
Education (years): <12 years	4 (2)
12 years	37 (22)
13-15 years	48 (29)
16 years	30 (18)
>16 years	47 (28)
Annual family income: <$15,000	14 (9)
$15-29,000	28 (18)
$30-49,000	35 (22)
$50-79,000	35 (22)
≥$80,000	44 (28)

	Disease characteristics
Stage: II	142 (86)
III	24 (14)
Surgery type: Lumpectomy	65 (39)
Mastectomy	101 (61)
Modified Radical	95 (57)
Radical	1 (1)
Elective Bilateral	5 (3)
Days since surgery (DSS):	M(SD) = 36(16.6)

Note. N = 166. Disease staging was based on the American Joint Committee on Cancer and the International Union Against Cancer staging systems. Days since surgery were calculated as the number of days between surgery and the initial assessment.

Table 3

Stress Measures Used

Objective (Stressors)

- Type of Life Events

1) Death or serious illness of a close friend or relative

2) Major financial difficulty

3) Divorce or other breakup involving family members (spouse) or close friends

4) Major conflict with children or grandchildren

5) Muggings, robberies, accidents, or similar events

- Total Number of Life Events

Subjective (Perceived Stress)

- Event Specific

1) Life Event Stress (Stress associated with life events)

2) Cancer Stress (Impact of Events Scale-IES)

- Global

1) Perceived Stress Scale (PSS-10)

Table 4

Number and Type of Life Events

Number of events reported	n (%)
0	44 (26)
1	70 (42)
2	26 (16)
3	18 (11)
4	7 (7)
5	1 (1)

Type of events reported	n (%)
Death or serious illness of close friend or relative	79 (38)
Major financial difficulty	45 (22)
Major conflict with children or grandchildren	30 (14)
Divorce or breakup involving family members/close friends	29 (14)
Muggings, robberies, accidents or similar events	25 (12)

Note. N = 166.

Table 5

Correlations among Objective Stressors (Life Events) and the Subjective Stress Measures

Measure	1	2	3	4	5	6	7	8	9	10	11
1. Death/Illness	1.00										
2. Finances	.08	1.00									
3. Conflict	-.01	.21**	1.00								
4. Crime/Accident	-.03	.20**	.20**	1.00							
5. Divorce/Breakup	.13*	.22**	.16*	.12	1.00						
6. # Events	.49****	.62****	.53****	.50****	.57****	1.00					
7. Event stress	.40****	.54****	.49****	.53****	.47****	.91****	1.00				
8. IES Total	.09	.09	.07	.05	.05	.13*	.13	1.00			
9. IES-A	.14*	.13*	.13*	.06	.10	.21**	.19**	.87****	1.00		
10. IES-I	.02	.08	-.01	.04	.00	.03	.04	.89****	.54****	1.00	
11. PSS-10	.02	.19**	.20**	.12	.14*	.24***	.29****	.51****	.51****	.38****	1.00

Note. 1. Death/Illness = Death or serious illness of a friend or close relative; 2. Finances = Major financial difficulty; 3. Conflict = Major conflict with children or grandchildren; 4. Crime/Accident = Muggings, robberies, accidents, or similar events; 5. Divorce/Breakup = Divorce or breakup involving family members or close friends; 6. # Events = Total number of life events.

*p ≤ 05. **p ≤ .01. ***p ≤ .001. ****p ≤ .0001.

Table 6

Correlations among Objective Stressors, Subjective Stress, and Depressive Symptoms

	CES-D	
Stress Measure	r	p
Objective (Stressors)		
Death or serious illness of close friend or relative	-.00	.49
Major financial difficulty	.18	.01
Divorce/breakup involving family members/close friends	.04	.31
Major conflict with children or grandchildren	.13	.05
Muggings, robberies, accidents, or similar event	.01	.46
Total number of life events	.16	.02
Subjective (Perceived Stress)		
Life Event Stress	.17	.01
Cancer Stress (IES-T)	.58	.0001
IES-A	.44	.0001
IES-I	.56	.0001
Global Stress (PSS-10)	.63	.0001

Table 7

Hierarchical Regression Results for the Prediction of Depressive Symptoms

Step	ΔR^2	$F(\Delta R^2)$	TR^2	$F(TR^2)$
1. Race	.035	5.89*	.035	5.89*
2. Neuroticism	.142	28.06**	.176	17.46**
3. Debt/Conflict	.022	2.20	.198	9.96**
4. IES-T	.216	59.13**	.415	22.67**
5. PSS-10	.099	32.47**	.514	28.02**

Note. N = 165. Abbreviations include: ΔR^2 = Change in squared multiple correlation; $F(\Delta R^2)$ = Value and significance of change in squared multiple correlation; TR^2 = Squared multiple correlation for total equation; $F(TR^2)$ = Value and significance of squared multiple correlation for total equation. Debt = major financial difficulty and Conflict = major conflict with children or grandchildren.

* $p < .01$. ** $p < .0001$.

Table 8

Results of Final Regression Model for the Prediction of Depressive Symptoms

Independent variable	Beta	t	sr^2
Race	-.108	-1.918*	.012
Neuroticism	.081	1.283	.005
Debt	.092	1.590	.008
Conflict	.006	.099	.000
IES-T	.330	5.097**	.079
PSS-10	.398	5.698**	.100

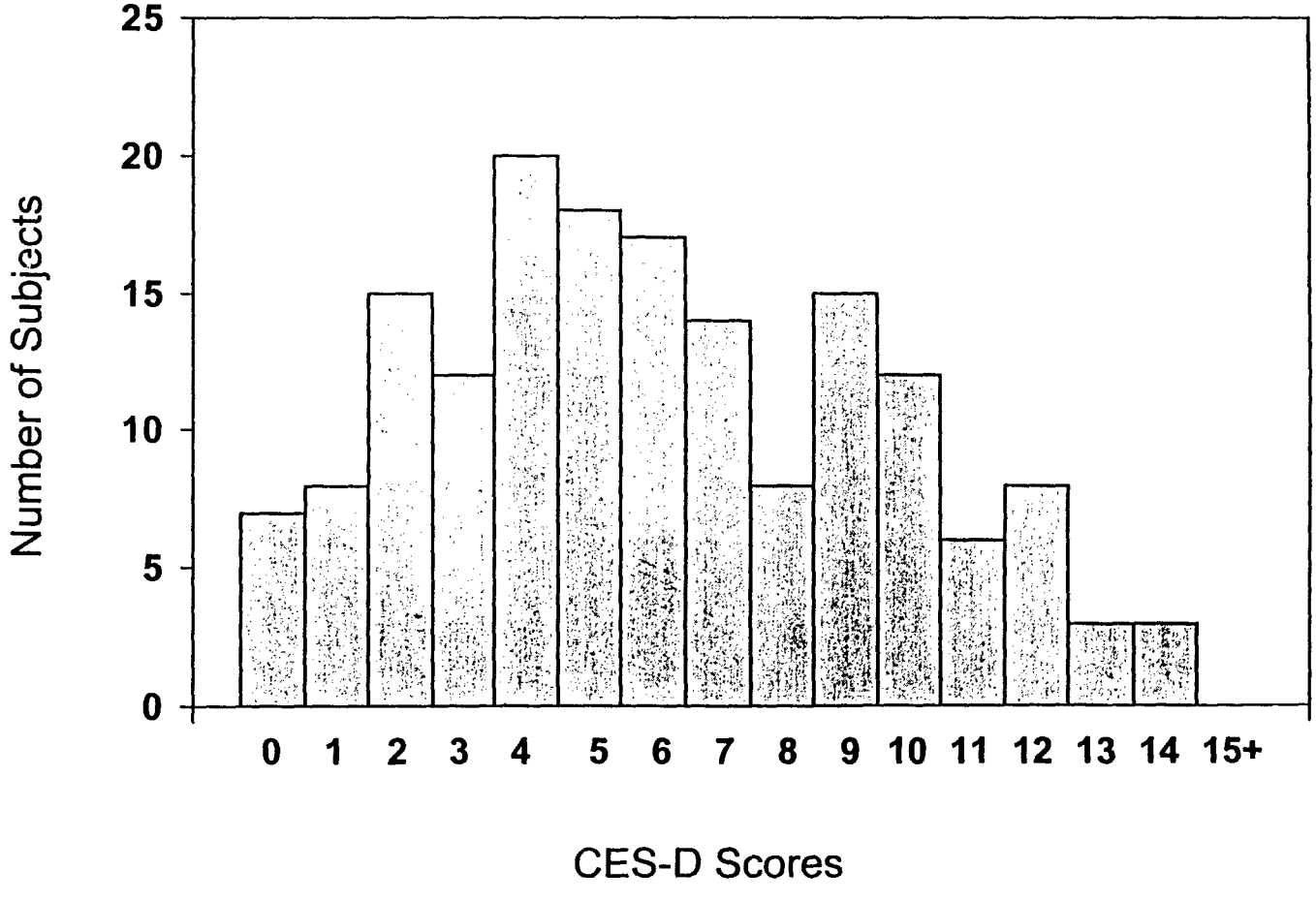
Note. N = 165. Abbreviations include: Debt = major financial difficulty and Conflict = major conflict with children or grandchildren.

* $p < .05$. ** $p < .0001$.

Figure Caption

Figure 1. Distribution of CES-D scores.

Figure 1


25
20
15
10
5
0
Number of Subjects
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15+
CES-D Scores

Breast cancer surgery:

Comparing surgical groups and determining individual differences in post operative sexuality and body change stress

Debora Yurek, William Farrar, and Barbara L. Andersen

Running head: Breast cancer surgery

Abstract

Women diagnosed and surgically treated for regional breast cancer (N = 190) were studied in the early post surgical period to determine the sexual and body change sequelae for women receiving modified radical mastectomy with breast reconstruction (MRMw/R) in comparison to the sequelae for women receiving breast conserving therapy (BCT) or modified radical mastectomy without breast reconstruction (MRM). The sexuality pattern for women receiving reconstructive surgery (MRMw/R) was one that was significantly different--with lower rates of activity and fewer signs of sexual responsiveness--than that for women in either of the other groups. Significantly higher levels of traumatic stress and situational distress regarding the breast changes were reported by the women receiving a modified radical mastectomy, whether or not they had undergone reconstruction, in contrast to the women treated with BCT. Finally, regression analyses, which controlled for menopausal status, prior behavior, and extent of disease and treatment, revealed that individual differences in sexual self schema were related to both sexual and body change stress outcomes.

Breast cancer surgery:

Comparing surgical groups and predicting post operative sexuality and body change stress

More than 180,000 women are diagnosed with breast cancer each year, and it is estimated that one in nine will develop the disease by age 85 (American Cancer Society: ACS, 1999). Surgery is usually the initial treatment. Surgery is usually the initial treatment for invasive breast cancer. Surgical options include a lumpectomy (breast conserving therapy, BCT) and axillary node dissection or a modified radical mastectomy (MRM) which includes removal of all breast tissue as well as the axillary lymph nodes. Not all women receiving a modified radical mastectomy are eligible for breast reconstruction (i.e. tissue expander with a permanent implant, autologous tissue transfer, or a permanent implant), but those that are may elect to receive it at the time of mastectomy. Still other women may elect to have a bilateral mastectomy (removal of the breast with the tumor as well as removal of the other, disease free, breast). Even though this is rare, women who request such extended surgery are typically those women with a strong familial history (i.e. a first degree relative, a mother, died of the disease at a young age), who are young when diagnosed (e.g. < 45 years), and who actively want to reduce their risk of recurrence, as the remaining breast is the most common site for disease progression (Harris, Morrow, & Bonadonna, 1993).

Clinical psychologists juxtapose these medical facts about breast cancer with concern about the psychological and behavioral sequelae of the disease. Since the earliest research on the psychological aspects of cancer, breast cancer surgery has been viewed as difficult, and, in some sense, traumatic. While cancer, per se, can be a devastating illness, disease in the breast was regarded as an especially difficult insult (e.g. Bard & Sutherland, 1955; Renneker & Cutler, 1952). Implicit was the notion that a woman (and perhaps her sexual partner) would see herself as a 'changed' sexual person following mastectomy. For example, in 1980 Derogatis offered a framework for two primary and "integrally related" components of sexual self-identity--sexuality

and body image--as being directly affected by diagnosis and treatment of breast cancer. Contemporary reviews highlight the importance of sexuality for cancer survivors, in general, as Gotay and Muraoka (1998) note: "The aspects of QoL (quality of life) that pose the most difficulty for survivors are likely to vary by cancer site, but this literature strongly implies that sexual functioning and/or satisfaction is a common issue for many survivors, regardless of diagnosis or treatment."

Conclusions such as the latter are familiar (e.g. Andersen, 1985), even though the methodologies for this research have been, at times, modest. Specifically, sexuality and body image constructs have been ill defined and operationalized, and difficult to assess as separate constructs (e.g., questionnaire items such as "I feel sexually attractive" are viewed as assessing both domains). Even so, a recent meta-analysis of psychosocial outcomes of breast cancer surgery separated the constructs and reported consistent psychologic advantages for the lumpectomy (i.e. breast conserving surgery) in contrast to mastectomy for body image and, to a lesser but still significant effect, for marital/sexual adjustment (Moyer, 1997). In fact, Moyer (1997) concluded: "The largest and most robust effect size, showing benefits for breast conserving surgery for body/self-image, is already a firmly established finding (pg 290)."

For those women who receive mastectomy, by choice or necessity, reconstructive surgery may be included. Since some types of reconstruction at the time of mastectomy may add additional cost and surgical morbidity (i.e. slower wound healing, extra days in hospital, added blood loss as well as anesthesia), research is needed to determine the benefit added. A certain motivation of reconstruction is for 'better' quality of life outcomes than with modified radical mastectomy alone. Thus, the first goal of the present research is to examine the post operative sexual and body image sequelae for women receiving modified radical mastectomy with immediate reconstruction (MRMw/R). Their responses are compared with the differential responses of the most studied surgical groups--women receiving either BCT or MRM only.

Related to this goal was our strategy to examine a broader conceptualization of the emotional distress and potential trauma surrounding breast changes. We included three

convergent, yet non-overlapping domains for assessment. First, the previous decades of research had included a measure of 'body image.' Although body image can be conceptualized in many ways, it is body satisfaction that has been frequently examined (e.g. Muth & Cash, 1997), and so a standard measure of *body satisfaction* (Berscheid, Walster, & Bohrnstedt, 1973) was included. Second, women receiving more extensive breast surgery report situational distress when their body is (or potentially might be) exposed; this distress may be greatest when a woman is with a sexual partner, but may also occur when she is alone (e.g. standing and dressing in front of a mirror; Beckmann et al, 1983; Kemeny et al., 1988; Margolis et al., 1990; Noguchi et al., 1993). Thus, we generated examples of *situational stressors* for the content of items. Third, intrusive thinking and avoidance are two important dimensions of the subjective stress response to traumatic stressors, and individuals who report involuntary, distress-related ruminations following traumatic life events are also those who suffer the greatest negative effects. This is true for war veterans or rape victims (Roszell, McFall, Malas, 1991; Keane & Wolfe, 1990) as well as breast cancer patients when they are assessed regarding their intrusive thoughts of cancer treatment or their avoidance of reminders of their disease (Cordova et al., 1995). Thus, we assessed traumatic stress--intrusive thoughts and avoidant behaviors--related to the breast changes. The three domains--traumatic stress, situational distress, and body satisfaction--were used to assess differential levels and opposing valences (i.e., positive body satisfaction versus negative subjective stress) of reactions to the body changes brought with the three types of breast cancer surgery (BCT, MRMw/R, and MRM).

In addition to describing the disease and/or treatment factors correlated with sexual and body image outcomes, our research tests theoretical models for the prediction of psychological/behavioral morbidity (e.g. Andersen, 1994; Andersen, Woods, & Copeland, 1997) and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994; Andersen, Farrar, Golden-Kreutz, Kutz, MacCallum, Courtney, & Glaser, 1998). This research step is important for progress in QoL research and for identification of women in greatest need for psychosocial care, and it is a step facilitated by the prior decades of psychological research (see Meyerowitz, 1980, as an example of

an early review). It is also timely, as upwards of 50% of women diagnosed with breast cancer will survive at least 15 years (ACS, 1999) and will, necessarily, "adjust" to surgical sequelae. Moreover, there is a current controversy surrounding the medical management of women identified to be at increased risk for the disease (Eisen & Weber, 1999) and the larger numbers of women diagnosed with non-invasive breast tumors (Stat bite, *Journal of the National Cancer Institute*, 1998). Some of the latter women receive aggressive surgical management. For example, Hartmann et al. (1999) studied women with a well defined family history of breast cancer who underwent a prophylactic bilateral mastectomy; their report, suggesting a reduction of at least 90% in both the incidence of breast cancer and risk of death from the disease, may well increase the frequency of women choosing such extensive surgical solutions to manage their risk for and fears about breast cancer.

For the prediction of psychological and behavioral morbidity surrounding sexual functioning, our model has included known correlates of sexuality for women (e.g., demographic factors, such as age; behavioral factors such as previous frequency of sexual intercourse; psychological factors such as level of sexual satisfaction) and health/illness variables (e.g., menopausal status, extent of disease and treatment; Andersen, 1994), but these variables do not fully account for who does and who does not experience significant sexual morbidity (e.g. Andersen, Anderson, & deProsse, 1989a). Individual differences appear to be important as well.

The construct of sexual self concept or sexual self-schema has been proposed (Andersen & Cyranowski, 1994; Andersen, Cyranowski, & Espindle, in press) and tested (Andersen, Woods, & Copeland, 1997) as an important individual difference variable. Sexual self-schema is a novel, cognitive view about sexual aspects of oneself. It functions not only as a quick referent of one's sexual history, but also as a point of origin for information--judgments, decisions, inferences, predictions, and behaviors--about the current and future sexual self. It regulates intrapersonal sexual processes, but sexual schema also appears to mediate the interpersonal aspects of sexual relationships. Those who differ in the valence of their sexual self views have very different sexual lives. Women with a positive sexual schema, for example, enter sexual relationships more

willingly, have a more extensive behavioral repertoire, evidence more positive emotions when in sexual relationships, and anticipate having positive sexual relationships in the future. Also, the affects and behaviors indicative of loving, intimate attachments are central to women with a positive sexual schema (Cyranowski & Andersen, 1998). In contrast, women with a negative sexual schema tend to describe themselves as emotionally cold or unromantic, and further, they are behaviorally inhibited in their sexual and romantic relationships. They may describe themselves as self-conscious, embarrassed, or inexperienced in sexual matters. Importantly, our longitudinal data indicate that these are stable self views, impervious, for example, to the passage of time or the waxing and waning of specific sexual or romantic relationships.

Thus, the second goal of this study is to test the contribution of sexual schema to women's post operative, sexual and body change outcomes. The test of the schema construct is framed within a conceptual model for predicting psychological and behavioral morbidity which controls for important, prior history variables (e.g. prior frequency of intercourse, menopausal status) and disease/treatment factors (Andersen, 1994). We hypothesize that individual differences in sexual self-schema can function as a diathesis, and they can be important in predicting sexual morbidity and/or dysfunction following the onset of a sexually-relevant stressor (see Cyranowski, Aarestad, & Andersen, in press for a complete discussion). Support for this general hypothesis was found with gynecologic cancer survivors (N = 61; Andersen, Woods, & Copeland, 1997). When comparisons were made with an age-matched sample of women without cancer, the expected disruption in sexuality was found for the women with cancer, due in part to the effects of their radical surgery and/or radiotherapy to the pelvis and genitals (e.g., Andersen, Anderson, & deProsse, 1989a). More relevant, however, was the finding that sexual self schema was a significant predictor of both post-treatment sexual behavior and responsiveness for the cancer survivors in analyses which controlled for pre-cancer levels of sexual behavior or responsiveness, extent of disease/treatment, and menopausal symptoms.

To enhance the clarity of the comparison of the surgery groups and rigor of the test of sexual schema, we obtained a homogeneous breast cancer sample and conducted the assessment at

a single, critical period. Women with regional malignant disease were selected as these women have a similar prognosis and adjuvant treatment trajectory. The timing of the assessment was controlled to reduce variability and, simultaneously, maximize the acute emotional distress accompanying the breast changes. That is, all women were assessed in the early post surgery/pre-adjuvant therapy period. These are the days when, for example, the chest wound has healed, women are visited by Reach to Recovery volunteers, and prostheses, if needed, are selected and first worn. This is, indeed, an early, critical period for women diagnosed with breast cancer (Rollin, 1976).

METHOD

Subjects

Participants were 190 women who had been diagnosed and surgically treated for stage II (87%) or stage III (13%) breast cancer. The staging schema of the American Joint Committee on Cancer and the International Union Against Cancer was used, and the obtained distribution corresponds to national trends for women with regional breast disease (ACS, 1999). Women were, on average, 36 days post surgery (range 5-101 days; SD = 16 days), and they had not yet begun their adjuvant therapy. The distribution of surgery type was the following: 78 (41%) women received lumpectomy or breast conserving therapy (BCT), 29 (15%) women received modified radical mastectomy with immediate reconstruction (MRMw/R), 79 (42%) women received modified radical mastectomy without breast reconstruction (MRM), and 4 (2%) women received elective bilateral mastectomy (BM). Women were anticipating the start of their adjuvant therapy [e.g. combinations of hormonal therapy (Tamoxifan), radiotherapy, chemotherapy, and/or chemotherapy followed by bone marrow transplantation] in the days following their accrual and assessment.

A demographic analysis revealed that the mean age for the participants was 51 years (range 30-84 years; SD = 11 years), the mean level of education was 15 years (some college), the annual personal income ranged from $2,000 to $200,000, annual family income ranged from $5,000 to $350,000, and 67% of the sample was employed outside the home. The racial distribution of the

group was 169 (89%) Caucasian, 19 (10%) African-American, and 2 (1%) Hispanic.

Marital/partner status of the sample was 65% married (mean of 22 years), but 72% were living with a partner. Nine percent (9%) of the women had never been married and 28% of the women were living alone. Of the partnered relationships, it appeared that all but 3 (2 lesbian and 1 bisexual), were heterosexual. The sexually active status of each woman at cancer diagnosis was determined. A women was defined as previously "sexually active" if she reported the occurrence of intercourse (or an equivalent intimate activity) at least once a month for the two months immediately preceding her diagnosis. Thus, 65% of the women were sexually active prior to diagnosis, and at the time of the assessment, 58% had resumed intercourse (or an equivalent form of intimacy) since surgery.

Measures

Individual Differences

The Sexual Self Schema Scale for Women was used (Andersen & Cyranowski, 1994). This scale contains 26 trait adjectives (e.g. cautious, loving, open-minded, experienced) plus 24 adjective fillers (e.g. generous, shallow, kind, practical) that are self-rated from 0 ("not at all descriptive of me") to 6 ("very descriptive of me"). Factor analytic studies reveal that the items tap three dimensions: (1) loving/romantic, (2) direct/open, and (3) embarrassment/conservatism. Items from factors 1 and 2 are summed and items from factor 3 are subtracted so that a total schema score can range from -42 to 102, with a numerically lower scores representing a negative sexual self view and higher scores reflecting a more positive sexual self view. Internal consistency for the scale is .70, and factor/total correlations range from .65 to .80. For this sample, the mean total schema score was 59 (range 14-89, SD = 13.31), comparable to that previously reported for healthy females (i.e., M = 60, SD = 14.15; Andersen & Cyranowski, 1994). Test retest reliability indicates stability, with 2 week estimates of .89, 2 month reliability of .88, and an 18 month reliability of .72. The measure predicts a wide range of sexual attitudes, behaviors, and responses (Cyranowski & Andersen, 1998) and cognitions (Cyranowski & Andersen, in press). Also, it is uncontaminated with social desirability or negative affect biases,

and process studies indicate that respondents are unaware that a sexual construct is being assessed (see Andersen & Cyranowski, 1994, for a complete discussion).

Sexuality.

Sexual behavior. Two types of data were obtained. (1) *Past sexual behavior* was assessed for the two months prior to diagnosis for the frequency of intercourse and the frequency of kissing. Each were rated using a ten point rating scale (ranging from 0 = this activity did not occur, 5 = three times per week, to 9 = this activity occurred more than 4 times a day). The items were summed. Data from female cancer and healthy samples indicate four month test retest reliability of .75 (Andersen & Broffitt, 1988), and ability of such items to distinguish cancer and healthy groups (e.g. Andersen, Woods, & Copeland, 1997).

(2) *Current sexual behaviors, including behaviors evidencing sexual approach as well as avoidance,* were assessed with a ten-point scale. Approach behaviors included affectionate kissing of partner, passionate ('deep') kissing of partner, erotic embrace, and kissing of sensitive (non-genital) areas, and were drawn from a factor analytic study (Andersen & Broffitt, 1988) of the Derogatis and Melisaratos (1979) Sexual Experience Scale. A current sexual behavior score was obtained by summing the respective items; internal consistency was .84. Total scores ranged from 0 to 34. Women also rated the frequency of sexually avoidant behavior (e.g. frequency of declining, refusing, or avoiding intercourse) since their breast surgery, and the avoidance score ranged from 0 to 7.

Sexual Response Cycle. A 27-item questionnaire assessing the psychophysiologic phases of the sexual response cycle was used. Items were drawn from a structured interview format (Andersen, Anderson, & deProsse, 1989a), but when used as a questionnaire the items had distinguished the responses of women with cancer versus healthy women (Andersen, Woods, & Copeland, 1997; Cyranowski & Andersen, 1998). Items for each phase of the response cycle--desire, excitement, orgasm and resolution--were included along with general satisfaction items. Women rated the frequency of the response/feelings on a five-point scale (ranging from 0 = never to 4 = always). A principle axis factor analysis, with an oblique (Harris Kaiser) rotation, reveals

three sexual response cycle factors--sexual desire, sexual arousal, and orgasm/resolution--with an additional factor for the general satisfaction items. Items assessing *desire* focused on sexual interest (e.g. How often were you not interested in your partner's suggestions for sex? How often did you desire sex?), ratings of *arousal* included physiologic markers (e.g. awareness of vaginal lubrication, feelings that the vagina was "too tight" for penetration, and pain or discomfort), while *orgasm /resolution* was assessed with indicators of climax (e.g. awareness of throbbing sensations in the vagina, feelings of body warmth, sweating, heavy breathing, rapid breathing) and the feelings of general relaxation, contentment, and tension release. Finally, four items assessed *general satisfaction* with sexuality (e.g. satisfaction with the frequency of sexual activity).

Negative valence items were reverse-scored prior to summing the items for a scale. Scores could range from 0 to 108 for total responsiveness (sum of all items), 0 to 24 for desire, 0 to 28 for arousal, 0 to 40 for orgasm/resolution, and 0 to 16 for general satisfaction. Internal consistency estimates for total responsiveness was .91, and those for each scale were .77 (desire), .80 (excitement), .86 (orgasm/resolution), and .72 (general satisfaction). Sexual response cycle factor intercorrelations ranged from .35 to .64, and the sexual response cycle correlations with the general satisfaction factor ranged from .48 to .66. For this sample, the mean scores were 70.7 (range 28 to 98) for total responsiveness, 12.9 for desire (range 0 to 21), 18.6 for arousal (range of 2 to 27), 28.1 for orgasm/resolution (range of 4 to 39), and 10.4 for general satisfaction (range of 4 to 16).

Global evaluation. A 9-point scale (ranging from 0 = could not be worse to 8 = could not be better, with 4 = average as the midpoint; Derogatis & Melisaratos, 1979) was used for women to rate their view of their sexual life prior to their cancer diagnosis. This global evaluation is sensitive to pre-to-post cancer treatment effects (e.g. Andersen, Anderson, & deProsse, 1989a; Andersen, Woods, & Copeland, 1997) and cancer groups (Andersen & Jochimsen, 1985). Scores ranged from 0 to 8 (M = 4.2; Md = 4.0; SD = 1.94).

Body change stress

Traumatic stress. Research investigating psychological reactions to stressful life events has

identified responses of intrusion and avoidance as characterizing peoples' subjective experience to the stressor. Intrusion has been typically operationalized as involuntary thoughts or images associated with the traumatic stressor, repetitive behaviors, or strong waves of distress-laden feelings (Allen, 1994), whereas avoidance responses have included measurement of behavioral inhibition related to the meanings and/or consequences of the event and emotional blunting (Keane & Wolfe, 1990).

For our purpose, change in physique due to breast cancer surgery was hypothesized as the traumatic life event. Thus, the 15-item Breast Impact of Treatment Scale (BITS) was developed to examine intrusive thoughts (9 items) and avoidant reactions (6 items) associated with breast changes. Patterned after the Impact of Events Scale (IES: Horowitz, Wilner & Alvarez, 1979), the item content was derived from prior breast cancer research assessing post-treatment concerns of women receiving breast surgery (e.g., avoidance of nudity, thoughts of disfigurement, feelings of body self-consciousness; Beckmann et al., 1983; Carver et al., 1994; Meyer & Aspegren, 1989; Pozo et al., 1992; Schain et al., 1983) but the items were worded to tap intrusive (e.g., "How my body has changed pops into my mind;" "When I see other women, I think that my body appears different than theirs.") and avoidant processes (e.g. "I don't want to deal with how my body looks;" "I avoid looking at or touching my scar.").

The internal structure of the BITS was examined using a principal components factor analysis with an oblique (Harris-Kaiser) rotation. On the basis of an eigenvalue scree plot and factor interpretability, a two-factor solution that accounted for 57% of the variance was extracted. The first factor was labeled "intrusion," and included nine items; the second factor, labeled "avoidance," included the remaining six items. Internal consistency was .88 for the Intrusion factor and .84 for the Avoidance factor; the factors correlated .70. Consistent with the scoring of the Impact of Events Scale (Horowitz, Wilner, & Alvarez, 1979), response choices were weighted (not at all = 0, rarely = 1, sometimes = 3, and often = 5) for the three degrees of positive endorsement of frequency. Items were summed to obtain subscale scores corresponding to Factor 1: Intrusion (range, 0 - 45), Factor 2: Avoidance (range, 0 - 30), and the total BITS score (range,

0 - 75) was calculated by summing the factor subscales. We found that the scale is uncontaminated by social desirability, as correlation with the Marlowe-Crowne Social Desirability scale (Crowne & Marlowe, 1960) was -.09. These data lend support to the internal validity of the Breast Impact of Treatment scale. For this sample, the mean values for the total score was 25.9 (range 0-67), the avoidance scale was 10.6 (range 0 to 33), and the intrusion scale was 15.3 (range 0-38).

Situational discomfort. Five situations typically reported as distressing to women following surgical treatment for breast cancer were generated. The content included looking at the chest while undressed, disrobing in front of a sexual partner, a sexual partner viewing the surgical site, and undressing in the presence of other women, and allowing others (e.g. women friends) to see the surgical site. Items such as these have differentiated women receiving alternative surgeries (see Bartelink et al., 1985; Beckmann et al., 1983; Kemeny et al., 1988; Margolis et al., 1990; Meyer & Aspegren, 1989; or Noguchi et al., 1993 for examples). A 5-point rating of distress (e.g. 0 = not at all distressed, 4 = extremely distressed) was used, and items were summed for a total distress score (range 0 - 20). Internal consistency was .86. Mean score among women in this sample was 6.3 (SD = 4.9, range 0-20).

Body satisfaction. The 10-item version (short form) of the Body Satisfaction Scale (BSS: Berscheid, Walster, & Bohrnstedt, 1973; Andersen & LeGrand, 1991) was used to assess satisfaction with the physical body (i.e. body parts) following surgical treatment. Factor analysis yields two factors: satisfaction with appearance [including facial and sexual parts (shape and size of breast/s and genitals)], and weight or body correlates of weight (hips, thighs, and buttocks; Andersen & LeGrand, 1991). In addition, a single item assessed satisfaction with overall appearance. Subjects rated the ten body items on a six-point satisfaction/dissatisfaction scale (i.e., 1 = extremely satisfied, 3 = satisfied, 6 = extremely dissatisfied), and higher scores indicated greater body dissatisfaction. Internal consistency was .84. A total Body Satisfaction score can be obtained by summing all items; the mean total score was 34.42 (range 10-58, SD = 7.96).

Procedures

Recruited consecutively from mid-1994 through mid 1999, the majority of the women

(81%) were being treated at a National Cancer Institute-designated, university-affiliated Comprehensive Center, and the remainder (19%) were receiving treatment at community hospitals within a 90 mile radius of the Cancer Center. All study participants were enrolled in a larger parent study, the Stress and Immunity Breast Cancer Project,[1] a randomized clinical trial.

Only women meeting the above disease stage and treatment schedule were eligible. Some women meeting criteria were excluded from participation for any of the following reasons: age < 20 or > 90 years; any previous cancer diagnosis; having begun adjuvant therapy; severe mental retardation; severe psychopathology (e.g. schizophrenia; non compliance with bipolar disorder treatment); dementia; or, other life threatening conditions (e.g. renal failure). Participation rates fluctuated over the course of the study depending on hospital factors (e.g. influx of new surgeons into the Department; relocation of the breast oncology outpatient clinic), but averaged 75%. Of those approached for participation, the major (top 3) reasons women gave for nonparticipation were insufficient time (29%), too far of a distance (e.g. > 40 miles from study hospital) to travel for participation (32%), and not interested (27%). Analyses of participants and refusers revealed no significant differences on sociodemographic (i.e. age, marital status, race) or disease/treatment relevant (i.e. menopausal status, estrogen receptor, stage, number of positive nodes, days since surgery) variables.

All participants came to the General Clinical Research Center at the university or a regional outpatient breast cancer clinic of the Cancer Center where psychologic, behavioral, and medical data were collected and a 60-ml blood sample was taken. The majority of the data for the present investigation were administered along with the questionnaire battery and structured interview as part of their initial assessment for the Stress and Immunity Study when accrual began; approximately 4 months into accrual the sexuality and body change stress assessment was expanded (i.e. sexual response cycle measure and impact of treatment measure were added) to complete the assessment; subjects were unaware of this addition to the assessment battery. Women were paid $30 for participation and reimbursed for their parking/transportation expenses (approx. $4). Following this initial assessment, women were randomized for the larger study and

then followed for future assessments.

RESULTS

Preliminary analyses

Descriptive analyses indicated that four women had received elective bilateral mastectomy. Because of the small numbers in this group, they were eliminated from all ANCOVA and regression analyses resulting in an N of 186. However, in the interest of providing clinical detail, we display their data in Table 1 along with that from the three-group comparisons (see Table 1).

Comparisons were made between the remaining surgical groups (BCT, MRMw/R, MRM) on variables that could potential covary with outcome. There were no significant differences ($p > .10$) between the groups on days since surgery or the sociodemographic variables of education, marital status, or race, although the groups differed significantly ($p < .001$) in age in years (BCT = 50, MRMw/R = 45, MRM = 54). Data suggest that younger women may report greater affective distress following breast cancer surgery (Ganz, Hirji, Sim, Coscarelli Schag, Fred, & Polinsky, 1993), and generational differences in sexual behavior have been reported (Lauman, Gagnon, Michael, & Michaels, 1994). Therefore, age was used as a covariate in the analyses described below.

Data for women who were not sexually active prior to surgery (i.e., denied having engaged in a sexually intimate activity such as intercourse at least once in the two months prior to surgery) were considered separately. Considering all reasons, 35% of the sample indicated that they were not sexually active prior to their diagnosis. The most common reason for sexual inactivity was the lack of an intimate partner (92%).

Analyses for the sexuality data were conducted using only the data from the 122 women reporting prior sexual activity, and thus the sample sizes were the following: BCT, n = 53; MRMw/R, n = 25; and MRM, n = 44). Considering this, there were no significant differences ($p's > .05$) between the sexually active women in the surgical groups on days since surgery or the sociodemographic variables of education, marital status, or race, but the groups differed significantly ($p < .05$) in age (BCT M = 48, MRMw/R = 45, MRM = 51). Again, age was used as

a covariate in the analyses for sexual outcomes.

Part 1: Comparison of surgical groups:

Modified Radical Mastectomy with Immediate Reconstruction (MRMw/R) vs Breast Conservation (BCT) or Modified Radical Mastectomy (MRM).

Sexual behavior

Assumptions of the group design employed here is that at an earlier point in time, prior to the diagnosis of cancer, the three surgical groups had comparable levels of sexual functioning and did not differ on dimensions that might covary with post surgical sexual outcome. To test these assumptions, we conducted a one way ANCOVA design (using age and education as the covariates) on the womens' reports of the frequency of intercourse, frequency of kissing, and their global evaluation of their sexual life for the period of 2 months prior to their cancer diagnosis. No significant group differences (p's > .10) were found. Grand means were the following: intercourse frequency = 3.14 (3 = once/week), kissing frequency = 6.90 (7 = once/day), and global evaluation = 4.71 (4 = average, 5 = above average). These data suggest that the sexually active women in the three surgical groups reported statistically equivalent levels of sexual behavior and satisfaction for the months immediately prior to their cancer diagnosis.

Analyses for approach and avoidance of sexual behaviors/activities were conducted. ANCOVA analyses for the measure of the frequency of current sexual activities was significant, $F(2, 101) = 4.23$, $p < .05$, and the Least Significant Difference test was used for follow up pair wise multiple comparisons (see Table 1 for mean scores across groups and multiple comparison results). They indicated that the frequency of current sexual behavior was significantly lower for the women receiving reconstruction (MRMw/R: $\underline{M} = 12.71$) than the frequency of behavior of women who received either lumpectomy (BCT: $\underline{M} = 18.06$) or MRM ($\underline{M} = 16.57$). Alternatively, the ANCOVA was not significant for the frequency of avoidant sexual activity. For related data we tested whether or not there was a differential rate of resumption of sexual intercourse following breast cancer surgery. The Pearson Chi Square was significant, $\chi^2 (2, N = 107) = 8.69$, $df = 2$, $p < .05$, and the rates of resuming intercourse for the groups are presented in Table 1. They indicate

that more of the women receiving BCT (87%) resumed intercourse than did women receiving modified radical mastectomy (57% and 68% for the MRMw/R and MRM groups, respectively).

For the sexual response cycle data, an ANCOVA was first conducted on the total score before proceeding with analyses for the subscales, and the ANCOVA for the total scale was significant $F(2, 55) = 3.40$, $p < .05$. Follow up ANCOVA's were then conducted for each subscale comprising the total score. The ANCOVA for the desire phase was not significant, although ANCOVA's for all remaining phases and general satisfaction were significant: arousal $F(2, 57) = 3.34$, $p < .05$; orgasm/resolution, $F(2, 63) = 5.62$, $p < .01$; and, general satisfaction $F(2, 65) = 4.37$, $p < .05$. Multiple comparisons indicated that for arousal, women treated with BCT reported significantly greater arousal during sexual activity than did women treated with MRM. For both orgasm/resolution and general satisfaction, follow up multiple comparisons indicated that the women receiving BCT and MRM reported significantly more signs and symptoms of orgasm and feelings of sexual satisfaction during their current sexual activity than did women receiving MRMw/R (see Table 1 for means).

Body change stress

Three aspects of body change were assessed: traumatic stress, situational distress, and, in contrast, self reports of body satisfaction. An ANCOVA (age as the covariate) was first conducted on the full scale score for the measure of traumatic stress and it was significant, $F(2, 148) = 19.62$, $p < .0001$. Therefor, follow up ANCOVA's for the intrusion $F(2, 153) = 20.20$, $p < .0001$, and avoidance $F(2, 149) = 9.83$, $p < .001$, scales were conducted and were also found to be significant. Multiple comparison analyses for the total score and the two subscales all yielded the same pattern of results (see Table 1 for means). That is, the lowest levels of traumatic stress, manifest by intrusive thoughts and avoidant behaviors regarding breast changes, were reported by the women receiving breast conserving treatment (BCT), whereas women receiving mastectomy, with reconstruction (MRMw/R) or without (MRM), reported significantly higher levels of traumatic stress. In fact, the scores for the mastectomy groups were more than one standard deviation above the mean of the scores for the BCT group.

The ANCOVA for the measure of situational distress was also significant, $F(2, 135) = 29.15$, $p < .0001$. Follow up multiple comparisons (see Table 1) indicated that women receiving BCT reported significantly less situational distress than women receiving MRM or MRMw/R.

The ANCOVA for the full scale score of the body satisfaction measure was also significant, $F(2, 176) = 3.76$, $p < .05$ (see Table 1 for descriptive data).

Part 2: Tests of the relationship between Sexual Self-Schema and sexual morbidity and body change stress

The above analyses indicate that women with breast cancer who received radical surgery, with or without reconstruction, experienced significantly greater sexual disruption and body change stress than did women who received more conservative surgical therapy (i.e. BCT), consistent with hypotheses concerning importance of the extent of disease/treatment for psychosocial outcomes (e.g. Andersen, 1994). The second goal of the research was to test the added contribution of a psychological individual difference variable, Sexual Self Schema, when evaluating sexual morbidity and body change stress. Preliminary one-way ANOVA's (Group: BCT, MRMw/R, MRM) were conducted and compared the surgical groups on the schema scores, and analyses for the total score as well as the three subscales were not significant (all p's > .05), indicating that sexual self schema did not covary with surgery group.

Variables were entered in regression analyses in the order proposed in previous papers on the prediction of post treatment sexual morbidity (i.e. Andersen, 1994; see Andersen, Woods, & Copeland, 1997 for an example). For the sexuality analyses, we entered the following variables: menopausal status [i.e. pre vs. post menopausal; this variable is relevant to genital sexual responses (e.g. Walling, Andersen, & Johnson, 1990) and, indirectly, it serves as a proxy for age]; sexual functioning prior to diagnosis (i.e. operationalized with the previous frequency of intercourse); stage of disease (i.e. stage II vs. stage III), extent of treatment (i.e. BCT vs. MRM vs. MRMw/R); and, finally, sexual self schema. For the body change analyses, the following variables were entered: menopausal status, stage of disease, extent of treatment, and, finally, sexual self schema. For the sexuality analyses, only data from women who were sexually active

prior to their diagnosis were used, and data from the entire sample was used for the body change analyses.

Sexuality

Two hierarchical multiple regression analyses were conducted to evaluate current sexual behaviors, both approach and avoidant. Both analyses produced comparable, significant findings and the results for both are provided in Table 2. As would be hypothesized from sexuality and cancer literatures, in the prediction of frequency of current sexual activity the menopause and prior frequency of intercourse control variables added significant incremental variance, as did the extent of the surgery variable. Following these, schema added an additional, significant, 3% of the variance, for a total of 32% of the variance accounted for by the predictors. In the analysis for avoidance of sexual activity, only the sexual self schema variable was a significant predictor, adding 8%, for a total of 8% of the variance accounted for by the predictor.

Regression analyses were conducted for the total score on the sexual response cycle measure (see Table 3). Here, the extent of surgery accounted for significant portion of variance, 4%, and then sexual schema adding an additional 12% of the variance, for a total of 31% of the variance accounted for by the predictors. Follow up regression analyses were conducted for the subscales for the response cycle measure and the data are displayed in Table 3. In each case, the analyses were significant and sexual self schema accounted for significant additional variance. Schema accounted for 11% of the variance in the total of 27% for sexual desire, 5% of the variance in the total of 27% for sexual arousal, and 4% of the variance in the total of 26% for orgasm/resolution.

Body Change Stress

Regression analyses were conducted with the three variables: traumatic stress, situational distress, and body satisfaction. The regression analysis with the total score on traumatic stress measure was significant, as were the follow up regression analyses for the Intrusion and Avoidance subscales. As the pattern of findings across the scales was similar, we provide for illustration in Table 4 the results for the total score. Of the control variables, only the extent of

surgery added significant incremental variance (21%), and sexual self schema added an additional 3%, for a total of 24% of the variance in traumatic stress accounted for by the predictors. Examining the subscales, sexual self schema accounted for an additional, significant 6% of the variance in the total of 18% for the Avoidance score, and 2% of the variance in the total of 25% for the Intrusion score.

The regression analysis for the prediction of the situational distress was also significant and results are displayed in Table 4. Of the control variables, the extent of surgery was most influential, accounting for a significant 30% of the variance. Moreover, sexual self schema accounted for an additional significant 3%, for a total of 35% of the variance in situational distress scores.

Finally, the regression analysis for the body satisfaction measure was not significant. In combination, the control and schema variables only accounted for 5% of the variance in the prediction of body satisfaction scores.

Discussion

In the recent decades, considerable discussion and change has taken place in oncology regarding the appropriate standard surgical therapy for women with breast cancer. Surgery has shifted from radical mastectomy, to modified radical mastectomy, to breast conserving surgery (lumpectomy) followed with radiotherapy. An impetus for clinical trials comparing the surgical therapies was to reduce morbidity (defined broadly, but including quality of life) without sacrificing cure rate. Currently, the data suggest that conservative surgery (i.e. BCT) with radiotherapy, produces comparable survival rates to that achieved with modified radical mastectomy for women with early stage disease (NIH Consensus Conference, 1991). However, not all women are eligible for BCT because of size/spread or location of the tumor and they must receive mastectomy, and still others, when given the choice, elect mastectomy. Subsequently, women are faced with the question of reconstruction: proceed or not, and if so, when? The circumstance of having options or choices regarding cancer treatment is the exception. When it does occur, psychological and behavioral data can be critically important, as individuals are

attempting to make the best choices to preserve, maintain, or, possibly, enhance, their future quality of life. Thus, these data provide an important perspective on this period of acute distress--the days and weeks immediately following breast cancer surgery.

The first goal of the research was to examine the post operative sexual and body change sequelae for women receiving modified radical mastectomy with immediate reconstruction (MRMw/R) in comparison to women receiving either BCT or MRM. Considering the sexual outcomes, the data suggest that the sexuality pattern for women receiving reconstructive surgery (MRMw/R) was one that was significantly different--with lower rates of activity and fewer signs of sexual responsiveness--than that for women receiving BCT and oftentimes lower than that for women receiving MRM without reconstruction as well. The behavioral disruption was particularly evident, as the level of current sexual activity for the women receiving reconstruction was more than one standard deviation below the means of the other groups; also, over 40% of the women had not yet resumed intercourse in the month intervening from surgery to the assessment. This represents a noticeable behavioral change, as women reported that prior to their diagnosis they had intercourse, on the average, of once per week. Considering the BCT and MRM groups, the finding of statistically equivalence between the groups for many of the sexual outcomes (e.g. current activity, orgasm/resolution, satisfaction) is consistent with the meta-analysis findings of Moyer (1997); she reported extremely small (and non significant) effect size differences between BCT and MRM groups, considering both randomized (ES = .06, ns) and nonrandomized (ES = .11, ns) investigations.

Comparison of the three groups on dimensions of body change stress reveals a consistent pattern of results for the three surgical groups, but one differing from the sexual outcomes previously discussed. Specifically, significantly higher levels of traumatic stress and situational distress regarding the breast changes were reported by all women treated with mastectomy (i.e. both MRM and MRMw/R) in contrast to the women treated with breast conservation (BCT). The pattern of less body change stress for women receiving BCT vs. MRM is not surprising. Indeed, this is a robust effect, found in both randomized and non randomized investigations, regardless of

whether or not the follow up interval is short or long (i.e. less than or greater than 12 months following surgery; Moyer, 1997). Many fewer studies have included a sample of women who have received reconstruction. The finding of equivalent levels of distress for both the MRMw/R and MRM groups, however, is consistent with data from cross sectional studies of heterogeneous samples of women assessed from 2 months to 2 years (Mock, 1993; Noguchi at al., 1993) following surgery as well as for longer than three years since surgery (Margolis, Goodman, & Rubin, 1990; Wellisch et al., 1989). Also, the data from the single study which randomized women to either BCT or MRMw/R (Schain et al., 1994) found better outcomes for the women randomized to BCT and no apparent body image benefit for the women receiving reconstruction.

In summary, the first goal of the research, to characterize the outcomes for women receiving breast reconstruction (MRMw/R), finds that their immediate postsurgery sexual behavior and sexual responses are disrupted, and significantly more so than women receiving lesser surgery (BCT) or comparable breast surgery but no reconstruction (MRM). Moreover, the data suggest that the reconstruction achieves no reduction in body change stress, at least when assessed during the early post surgery period, as the reconstruction group reported levels of stress equivalent to those of the women receiving MRM only, and both mastectomy groups reported body change stress significantly higher (in some cases twice as high) as the responses of the women receiving BCT. We also provided descriptive data on the few women who requested bilateral mastectomy. Even though additional numbers of women are necessary to document the reliability of these estimates, the values are consistent with the hypothesis that more radical surgical therapy does, indeed, result in greater psychological and behavioral morbidity. These women report significant situational distress and avoidant behaviors (e.g. avoiding looking at her chest, turning away from her sexual partner).

The second goal of the research was to test the contribution of a psychological variable--sexual self schema--to sexual and body change outcomes. Our intent was to make this a difficult test, as we were aware of the powerful role that prior levels of sexual behavior have in predicting sexual activity, as well as the important role that cancer treatments can have in effecting quality of

life. Indeed, the latter factors are regarded as so important that individual differences are rarely considered, even in the case of Phase III cancer clinical trials (i.e. randomized trials comparing treatments thought to differ in efficacy) which are believed to produce, a priori, differential quality of life outcomes (e.g. Moinpour et al., 1998). In the regression analyses for both sexuality and body change stress, sexual self schema consistently added significant, incremental variance beyond that explained by the control variables, many of which were important contributors, as hypothesized. Thus, it would appear that women with more negative sexual self views are more apt to engage in lower levels of sexual activity, have difficulties with their sexual responsiveness, and be vulnerable to heightened body change stress. The common characteristics of negative schema women--lower sexual arousability, greater sexual embarrassment and negativity--are likely contributors to make them vulnerable to coping poorly with the breast changes and disruption of sexual intercourse brought on with the cancer stress, hospitalization, and recovery. Moreover, this psychological difference among women plays an important role even when other powerful factors--such as the extent of the surgery--are considered. The importance of sexual schema found here replicates our initial test of sexual self schema predicting sexual outcomes for gynecologic cancer survivors (Andersen, Woods, & Copeland, 1997).

Considering the clinical utility of this finding, one future use of the schema measure might be to test its use as a screening measure to identify women at greatest risk for quality of life disruption in the domains of sexuality or body change following breast surgery. Indeed, in an era of shrinking resources for health care services of all types, preventive efforts which target psychosocial care to those in greatest need are important. For example, these data suggest that post menopausal women receiving MRM (with or without reconstruction), and those with more negative sexual self schemas, are at heightened risk for sexual disruption and body change stress. Importantly, clinical psychologists have several effective strategies to reduce sexual and body related anxieties (e.g. see Wincze & Carey, 1991) that have applicability to female cancer survivors and their partners (see also Andersen & Elliot, 1993).

This study offered a novel conceptualization of the emotional distress, and perhaps trauma,

surrounding breast changes. As we noted, womens' reports of distress due to a changed 'body image' (however defined) have been long standing and robust, despite nebulous measurement strategies. Even though we found group differences here, measures of "satisfaction" with body parts have been inconsistent in their ability to document change following cancer treatments (e.g. Andersen & LeGrand, 1991; Langer, Prohaska, Schreiner-Frech, Ringlelr, & Kubista, 1991), suggesting that "satisfaction-dissatisfaction" scales or ratings of body parts may not be the most appropriate measurement strategies or conceptualization for the concerns of women undergoing significant breast changes. Indeed, womens' endorsements of avoidance behaviors and intrusive thoughts would suggest that the stress of this experience can at least mimic (if not be identical to) the psychological remnants of a traumatic stressor. As with many traumatic stressors, the occurrence of uncontrollable events (e.g. intrusive thoughts "popping into awareness"), likely heighten the levels of womens' general distress as well. Still, there may be important phenomenological differences between the traumatic body change stress of breast cancer and the psychological trauma of other stressors (e.g. rape, war). For example, the body change stressor for women treated for breast cancer remains (i.e. the chest is permanently changed) and other less tangible aspects (e.g. the fear of recurrence and death) remains to be faced each day. For now, the strategy of conceptualizing breast changes as a precipitant to significant stress-related responses (i.e. behavioral avoidance, intrusive thoughts) appears to produce useful data. In addition, this conceptualization and measurement strategy suggest directions for choosing psychological interventions (e.g. anxiety reduction techniques for avoidant behaviors; cognitive behavioral strategies for problematic thoughts) to treat women with clinical levels of body change stress.

Finally, we note particular methodologic aspects of this study. The sample is predominantly Caucasian, and so generalizability of the findings to other ethnic groups may be limited. The large, homogeneous sample and control of the timing of the assessment at a critical period were important design features, as we were able to differentiate psychological and behavioral sequelae for the three surgeries and test for individual differences in outcomes. Although an important strength was control over the timing of the assessment (i.e. the data

document the sexual and body change stress in the early surgical recovery period), continued follow up data are necessary to document the reliability of these changes for later follow up. However, our longitudinal data with gynecologic cancer patients indicated that to the extent that sexual problems develop early in the recovery period, the majority of them do not resolve during the following year, and, in addition, some women who resume intercourse still develop sexual problems at a later time (Andersen, Anderson, & deProsse, 1989b). However, we will need to follow the current sample to determine if this is their scenario too, or instead, their sexual activity returns to former levels and their body change stress declines.

To some, the difficult outcomes for the women receiving reconstruction may surprising. However, consideration of the technical and clinical aspects of reconstruction may be informative (see Brown, 1991 for a more complete discussion of patient concerns). For example, reconstruction with an implant produces a breast "mound" without a breast nipple. Also, breast implants do not have the same tactile sensation, as the implanted breast can feel "hard" compared to one's other breast. These, and related experiences, are the outcomes to which women undergoing reconstruction were adjusting at the time of our assessment. However, as the woman becomes more familiar with these qualities of the breast, there may be some reduction in stress. In addition, women with reconstruction do, indeed, experience what many report as the main benefits of reconstruction -- greater ease in clothing style and convenience--and the escape from wearing a prosthesis. Whether or not these or other benefits occur and are of sufficient importance to allow women who under went reconstruction to become less avoidant, more sexually responsive, and less vulnerable to intrusive, stressful thoughts remains to be discovered. What is clear, however, is that women at risk for such difficulties can be identified at the time of surgery, and effective sexual and cognitive behavior therapies exist to prevent or minimize the types of or magnitude of psychosocial and quality of life disruptions shown here. To the extent that clinical psychologists and other behavioral scientists can provide data to forecast quality of life outcomes, they will have provided a mechanism and pathway to prevent stress from the breast cancer experience.

References

Allen, S. N. (1994). Psychological assessment of post-traumatic stress disorder: Psychometrics, current trends, and future directions. *Psychiatric Clinics of North America, 17 (2),* 327-349.

American Cancer Society (1999). *Cancer Facts & Figures -- 1999.* Atlanta, GA: ACS.

Andersen, B. L. (1994). Surviving cancer. *Cancer, 74,* 1484-1495.

Andersen, B. L. (1985). Sexual functioning morbidity among cancer survivors: Current status and future research directions. *Cancer, 55,* 1835-1842.

Andersen, B. L., Anderson, B., & deProsse, C. (1989a). Controlled Prospective longitudinal study of women with cancer: I. Sexual functioning outcomes. *Journal of Consulting and Clinical Psychology, 57 (6),* 683-691.

Andersen, B. L., Anderson, B., & deProsse, C. (1989b). Controlled Prospective longitudinal study of women with cancer: II. Psychological outcomes. *Journal of Consulting and Clinical Psychology, 6,* 692-697.

Andersen, B. L. & Broffitt, B. (1988). Is there a reliable and valid self-report measure of sexual behavior? *Archives of Sexual Behavior, 17 (6),* 509-525.

Andersen, B. L. & Cyranowski, J. M. (1994). Women's sexual self schema. *Journal of Personality and Social Psychology, 67 (6),* 1079-1100.

Andersen, B.L., & Cyranowski, J.C., & Espindle, D. (1999). Men's sexual self schema. *Journal of Personality and Social Psychology, 76,* 645-661.

Andersen, B.L., & Elliot, M.L. (1993). Sexuality for women with cancer: Assessment, theory, and treatment. *Sexuality and Disability, 11,* 7-37).

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D., Kutz, L.A., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress and immune responses following surgical treatment of regional breast cancer. *Journal of the National Cancer Institute,* 90 (1), 30-36.

Andersen, B.L., & Jochimsen, P.R. (1985). Sexual functioning among breast cancer, gynecologic cancer, and healthy women. *Journal of Consulting and Clinical Psychology, 53,* 25-32.

Andersen, B.L., Kiecolt-Glaser, J.K., & Glaser, R. (1994). A biobehavioral model of cancer stress and disease course. *American Psychologist, 49,* 389-404.

Andersen B. L. & LeGrand, J. (1991). Body image for women: Conceptualization, assessment, and a test of its importance to sexual dysfunction and medical illness. *The Journal of Sex Research, 28 (3),* 457-477.

Andersen, B. L., Woods, X., & Copeland, L. (1997). Sexual self schema and sexual morbidity among gynecologic cancer survivors. *Journal of Consulting and Clinical Psychology,* 65, 221-229.

Bard, M. & Sutherland, A. M. (1955). Psychological impact of cancer and its treatment: IV. Adaptation to radical mastectomy. *Cancer, 4,* 656-672.

Bartelink, H., van Dam, F., & van Dongen, J. (1985). Psychological effects of breast conserving therapy in comparison with radical mastectomy. *International Journal of Radiation Oncology Biology and Physics, 11,* 381-385.

Beckmann, J., Johansen, L., & Blichert-Toft, M. (1983). Psychological reactions in younger women operated on for breast cancer. *Danish Medical Bulletin, 30 (2),* 10-16.

Berscheid, E., Walster, E., & Bohrnstedt, G. (1973). The happy American body: A survey report. *Psychology Today, 7,* 119-131.

Brown, H.G. (1991). Patient issues in breast reconstruction. *Cancer, 68,* 1167-1169.

Carver, C. S., Pozo-Kaderman, C., Harris, S. D., Noriega, V., Scheier, M. F., Robinson, D. S., Ketcham, A. S., Moffat, R. L., & Clark, K. C. (1994). Optimism versus pessimism predicts the quality of women's adjustment to early stage breast cancer. *Cancer, 73 (4),* 1213-1220.

Crowne, D. P. & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology, 24 (4),* 349-354.

Cordova, M. J., Andrykowski, M. A., Redd, W. H., Kenady, D. E., McGrath, P. C., & Sloan, D. A. (1995). Frequency and correlates of posttraumatic-stress-disorder-like symptoms after treatment for breast cancer. *Journal of Consulting and Clinical Psychology, 63 (6),*

981-986.

Cyranowski, J.C., Aarestad, S.L., & Andersen, B.L. (in press). The role of sexual self schemas in a diathesis-stress model of sexual dysfunction. *Applied and Preventive Psychology.*

Cyranowski, J.C., & Andersen, B.L. (1998). Schemas, sexuality, and romantic attachment. *Journal of Personality and Social Psychology, 74,* 1364-1379.

Cyranowski, J.M., & Andersen, B.L. (in press). Evidence of self-schematic cognitive processing in women with differing sexual self-views. *Journal of Social and Clinical Psychology.*

Derogatis, L.R., & Melisaratos, N. (1979). The DSFI: A multidimensional measure of sexual functioning. *Journal of Sex and Marital Therapy, 5,* 244-281.

Doerfler, L. A., Pbert, L., & DeCosimo, D. (1994). Symptoms of posttraumatic stress disorder following myocardial infarction and coronary artery bypass surgery. *General Hospital Psychiatry, 16,* 193-199.

Eisen, A., & Weber, B.L. (1999). Prophylactic mastectomy--The price of fear. *The New England Journal of Medicine, 340 (2),* 10-11.

Ganz, P.A., Hirji, K., Sim, M.-S., Coscarelli Schag, C.A., Fred, C., & Polinsky, M.L. (1993). Predicting psychosocial risk in patients with breast cancer. *Medical Care, 31,* 419-431.

Gotay, C.C., & Muraoka, M.Y. (1998). Quality of life in long-term survivors of adult-onset cancers. *Journal of the National Cancer Institute, 90,* 656-667.

Harris, J. R., Morrow, M., & Bonadonna, G. (1993).Cancer of the breast. In V. T. DeVita, S. Hellman, & S. A. Rosenberg (Eds.) *Cancer: Principles and Practice of Oncology, 4th Edition* (pp. 1264-1332). Philadelphia: J. B. Lippincott Company.

Hartmann, L.C., Schaid, D.J., Woods, J.E., Crotty, T.P., Myers, J.L., Arnold, P.G., Petty, P.M., Sellers, T.A., Johnson, J.L., McDonnell, S.K., Frost, M.H., Jenkins, R.B., Grant, C.S., & Michels, V.V. (1999). Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *The New England Journal of Medicine, 340 (2),* 77-84.

Horowitz, M., Wilner, N., & Alvarez, W. (1979). Impact of events scale: A measure of subjective stress. *Psychosomatic Medicine, 41 (3),* 209-218.

Kemeny, M. M., Wellisch, D. K., & Schain, W. S. (1988). Psychosocial outcome in a randomized surgical trial for treatment of primary breast cancer. *Cancer, 62,* 1231-1237.

Keane,T.M., & Wolfe, J. (1990). Comorbidity in posttraumatic stress disorder: An analysis of community and clinical studies. *Journal of Applied Social Psychology, 20,* 1776-1788.

Langer, M., Prohaska, R., Schreiner-Frech, I., Ringler, M., & Kubista, E. (1991). Coping and body image after different operative techniques in breast cancer patients. *Psychotherapie Psychosomatik Medizinishe Psycholigie, 41,* 379-384.

Laumann, E.O., Gagnon, J.H., Michael, R.T., & Michaels, S. (1994). *The social organization of sexuality: Sexual practices in the United States.* Chicago: The University of Chicago Press.

Margolis, G. J. & Goodman, R. L. (1984). Psychological factors in women choosing radiation therapy for breast cancer. *Psychosomatics, 25 (6),* 464-469.

Margolis, G. J., Goodman, R. L., & Rubin, A. (1990). Psychological effects of breast-conserving cancer treatment and mastectomy. *Psychosomatics, 31 (1),* 33-39.

Meyer, L., & Aspegren, K. (1989). Long-term psychological sequelae of mastectomy and breast conserving treatment for breast cancer. *Acta Oncologiaca, 28,* 13-18.

Meyerowitz, B.E. (1980). Psychological correlates of breast cancer and its treatments. *Psychological Bulletin, 87,* 108-131.

Mock, V. (1993). Body image in women treated for breast cancer. *Nursing Research, 42 (3),* 153-157.

Moinpour, C.M., Savage, M.J., Troxel, A., Lovato, L.C., Eisenberger, M., Veith, R.W., Higgins, B., Skeel, R., Yee, M., Blumenstein, B.A., Crawford, E.D., & Meyskens, F.L. (1998). Quality of life in advanced prostate cancer: Results of a randomized therapeutic trial. *Journal of the National Cancer Institute, 90,* 1537-44.

Moyer, A. (1997). Psychosocial outcomes of breast-conserving surgery versus mastectomy: A

meta-analytic review. *Health Psychology, 16,* 3, 284-298.

Muth, J.L., & Cash, T.J. (1997). Body-image attitudes: What difference does gender make? *Journal of Applied Social Psychology, 27,* 1438-1452.

National Institute for Health Consensus Conference. (1991). Treatment of early stage breast cancer. *Journal of the American Medical Association, 265,* 391-395.

Noguchi, M., Saito, Y., Nishijima, H., Koyanagi, M., Nonomura, A., Mizukami, Y., Nakamura, S., Michigishi, T., Ohta, N., Kitagawa, H., Earashi, M., Thomas, M., & Miyazaki, I. (1993). The psychological and cosmetic aspects of breast conserving therapy compared with radical mastectomy. *Surgery Today, 23,* 598-602.

Pozo, C., Carver, C. S., Noriega, V., Harris, S. D., Robinson, D. S., Ketcham, A. S., Legaspi, A., Moffat, F. L., & Clark, K. C. (1992). Effects of mastectomy versus lumpectomy on emotional adjustment to breast cancer: A prospective study of the first year post surgery. *Journal of Clinical Oncology, 10 (8),* 1292-1298.

Renneker, R. & Cutler, M. (1952). Psychological problems of adjustment to cancer of the breast. *Journal of the American Medical Association, 148 (10),* 833-838.

Rollin, B. (1976). *First, you cry.* Philadelphia: Lippincott.

Roszell, D., McFall, M., & Malas, K. (1991). Frequency of symptoms and concurrent psychiatric disorder in Vietnam veterans with chronic PTSD. *Hospital Community P`sychiatry, 42,* 293-296.

Schain, W., Edwards, B. K., Gorrell, C., de Moss, E. V., Lippman, M. E., Gerber, L. H., & Lichter, A. S. (1983). Psychosocial and physical outcomes of primary breast cancer therapy: Mastectomy vs excisional biopsy and irradiation. *Breast Cancer Research and Treatment, 3,* 377-382.

Schain, W. S., d'Angelo, T. M., Dunn, M. E., Lichter, A. S., & Pierce, L. J. (1994). Mastectomy versus conservative surgery and radiation therapy. *Cancer, 73 (4),* 1221-1228.

Stat bite: Change in breast cancer incidence by stage. (1988). *Journal of the National Cancer*

Institute, 90 (19), 1429.

Walling, M.K., Andersen, B.L., & Johnson, S.R. (1990). Hormonal replacement therapy for postmenopausal women: A review of sexual outcomes and related gynecologic effects. *Archives of Sexual Behavior, 19,* 119-137.

Wellisch, D.K., DiMatteo, R., Silverstein, M., Landsverk, J., Hoffman, R., Waisman, J., Handel, N., Waisman-Smith, E., & Schain, W. (1989). Psychosocial outcomes of breast cancer therapies: Lumpectomy versus mastectomy. *Psychosomatics, 30,* 365-373.

Wincze, J.P., & Carey, M.P. (1991). *Sexual dysfunction: A guide for assessment and treatment.* New York: The Guilford Press.

Author notes

Debora Yurek, Department of Psychology (now at Malstrom Air Force Base, Grand Forks, N.D.); William Farrar, Department of Surgery; and, Barbara L. Andersen, Department of Psychology.

The Stress and Immunity Breast Cancer Project is an ongoing study conducted at the Department of Psychology and the James Cancer Hospital and Research Institute at The Ohio State University, Columbus, Ohio. The study is supported by grants from the American Cancer Society (PBR-89), the Longaberger Company-American Cancer Society Grant for Breast Cancer Research (PBR-89A), the U.S. Army Medical Research Acquisition Activity Grants (DAMD17-94-J-4165 and DAMD17-96-1-6294), and the National Institutes of Mental Health (1 RO1 MH51487). This research was also supported in part by the General Clinical Research Center (MO1-RR0034), the Ohio State University Comprehensive Cancer Center Core Grant from the National Cancer Institute (P30 CA16058), and the Department of Psychology and the College of Social and Behavioral Sciences at The Ohio State University. We thank the study participants for their time and assistance. In addition, we thank the following individuals for their contributions: Research/graduate assistants Susan Aarestad, Elizabeth Street Bromet, Nicole Chaput, Angela Collier, Larisa Demshuk, Melissa Douglas, Georita Frierson, Sarah Grimes, Katheryn Pingel, Jessica Walker, Laura Wielonski, and nurse Beth Putz for conducting the psychological/nursing assessments; surgical oncologists Drs. William Burak, William Carson, Julian Kim, Gregory LaValle, Deborah Martinez, Michael Walker, and Lisa Yee, and medical oncologists Drs. Kelly Cawley, Chris Rhoades, Arthur Sagone, Victoria Seewalt, Michael Stanek, and James Ungerleider for accrual; Drs. Mary Elizabeth Courtney and Mary DeLamatre for data management and Deanna Golden-Kreutz, Vicki DiLillo, and Ms. Laura Peterson for project management; Drs. Jill Cyranowski, Steve Beck, Mark Elliot, Charles Emery, and Robert McCallum for helpful comments on the manuscript. These data are in partial fulfillment of the dissertation requirements for the first author.

Correspondence concerning this article should be addressed to Barbara L. Andersen,

Department of Psychology, 1885 Neil Avenue, The Ohio State University, Columbus, OH 43210-1222. Electronic mail may be sent via Internet to andersen.1@osu.edu.

Footnote

[1]Data from the first 116 women accrued to the Stress and Immunity Breast Cancer Project (including 116 of the 190 women included here) have been published (Andersen et al., 1998). The latter paper documented a negative relationship between stress and immunity; there is no overlap of measures between Andersen et al. (1998) and the present report.

Table 1

Adjusted Mean Scores For Four Surgical Groups For Measures Of Sexuality And Body Change Stress and ANCOVA And Multiple Comparison Results For Three Surgical Groups.

Area / Subarea	Surgical Group: Breast Conserving Therapy	Mod. Rad. Mastec. w/ Reconstruction	Modified Radical Mastectomy	Bilateral Mastectomy
Sexual behavior				
Current activity*	18.06[a]	12.71[b]	16.57[a]	16.67
Avoidant activity	.91	.81	1.32	—
Resume intercourse*	87%[a]	57%[b]	68%[b]	33%
Sexual response cycle*	76.29[a]	63.83	70.64[b]	----
Desire (absence of)	13.03	12.14	12.85	—
Arousal*	20.60[a]	17.85	16.39[b]	—
Orgasm/Resolution**	30.56[a]	24.46[b]	29.62[a]	—
General satisfaction*	11.34[a]	9.02[b]	10.86[a]	--
Body Change Stress				
Traumatic stress***	17.86[a]	32.71[b]	31.36[b]	37.67
Avoidance***	7.95[a]	13.12[b]	12.00[b]	18.33
Intrusion***	10.28[a]	19.56[b]	19.02[b]	19.33
Situational distress***	3.29[a]	8.60[b]	8.63[b]	10.50
Body (dis)satisfaction*	33.38[a]	32.28[a]	36.39[b]	32.00

Note: Groups are Breast conservation therapy (BCT), Modified radical mastectomy with reconstruction (MRMw/R), Modified radical mastectomy (MRM), and Bilateral mastectomy (BiM). For the outcomes, a higher score indicates a greater level of behavior/response. Different superscripts indicate significant

differences ($p < .05$) for the multiple comparison tests comparing the BCT, MRMw/R, and MRM groups. - = insufficient data. * = $p < .05$. ** = $p < .01$. *** = $p < .001$.

Table 2

Hierarchical Regression Analyses Testing Model of Morbidity (Andersen, 1994) and Sexual Self Schema in Relationship to Sexual Behavior Outcomes

Step	Predictor	Beta	R	R^2	t	df
		Predicted Outcome: Frequency of current sexual activity				
1	Menopausal status	-.21	.24	.06	-2.50**	(1,104)
2	Prior freq. of intercourse	.32	.45	.20	3.69***	(1,103)
3	Stage of disease	-.01	.45	.20	-.06	(1,102)
4	Extent of treatment	.35	.54	.29	3.13**	(2,100)
		.27			2.36*	
5	Sexual self schema	.18	.57	.32	2.08*	(1, 99)
		Predicted Outcome: Avoidance of sexual activity				
1	Menopausal status	-.13	.12	.01	-1.35	(1,106)
2	Prior freq. of intercourse	.06	.12	.01	.58	(1,105)
3	Stage of disease	.03	.13	.02	.31	(1,104)
4	Extent of treatment	.06	.16	.03	.44	(2,102)
		.15			1.12	
5	Sexual self schema	-.24	.29	.08	-2.44*	(1, 101)

Table 3

Hierarchical Regression Analyses Testing Model of Morbidity (Andersen, 1994) and Sexual Self Schema in Relationship to Sexual Response Cycle Outcomes

Step	Predictor	Beta	R	R^2	t	df
		Predicted Outcome: Total sexual responsiveness				
1	Menopausal status	-.16	.17	.03	-1.39	(1, 58)
2	Prior freq. of intercourse	.04	.20	.04	.30	(1, 57)
3	Stage of disease	-.13	.24	.06	-1.06	(1, 56)
4	Extent of treatment	.39	.44	.19	2.52*	(2, 54)
		.31			1.95*	
5	Sexual self schema	.36	.56	.31	3.01***	(1, 53)
		Predicted Outcome: Sexual desire				
1	Menopausal status	-.27	.27	.07	-2.56**	(1, 76)
2	Prior freq. of intercourse	.18	.37	.14	1.65	(1, 75)
3	Stage of disease	-.01	.37	.14	-.09	(1, 74)
4	Extent of treatment	.07	.40	.16	.51	(2, 72)
		.15			1.05	
5	Sexual self schema	.34	.52	.27	3.19**	(1, 71)
		Predicted Outcome: Sexual arousal				
1	Menopausal status	-.32	.35	.13	-3.47**	(1, 60)
2	Prior freq. of intercourse	.05	.37	.14	1.52	(1, 59)
3	Stage of disease	-.09	.39	.15	-.76	(1, 58)
4	Extent of treatment	.20	.45	.21	1.59	(2, 56)
		.01			.03	
5	Sexual self schema	.113	.52	.27	2.27*	(1, 55)

Table 3 cont.

Hierarchical Regression Analyses Testing Model of Morbidity (Andersen, 1994) and Sexual Self Schema in Relationship to Sexual Response Cycle Outcomes

Step	Predictor	Beta	R	R^2	t	df
		Predicted Outcome: Orgasm/Resolution				
1	Menopausal status	-.10	.08	.01	-.86	(1, 66)
2	Prior freq. of intercourse	.00	.09	.01	-.03	(1, 65)
3	Stage of disease	-.11	.14	.02	-.98	(1, 64)
4	Extent of treatment	.51	.46	.21	3.38***	(2, 62)
		.46			3.02**	
5	Sexual self schema	.23	.51	.26	2.01*	(1, 61)

Note. *p < .05. **p < .01. *** p < .001.

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF

MCMR-RMI-S (70-1y) 26 Aug 02

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

ADB274369
ADB256383
ADB264003
ADB274462
ADB266221
ADB274470
ADB266221
ADB274464
ADB259044
ADB258808
ADB266026
ADB274658
ADB258831
ADB266077
ADB274348
ADB274273
ADB258193
ADB274516
ADB259018
ADB231912
ADB244626
ADB256677
ADB229447
ADB240218
ADB258619
ADB259398
ADB275140
ADB240473
ADB254579
ADB277040
ADB249647
ADB275184
ADB259035
ADB244774
ADB258195
ADB244675
ADB257208
ADB267108
ADB244889
ADB257384
ADB270660
ADB274493
ADB261527
ADB274286
ADB274269
ADB274592
ADB274604
ADB274596
ADB258952
ADB265976
ADB274350
ADB274346
ADB257408
ADB274474
ADB260285
ADB274568
ADB266076
ADB274441
ADB253499
ADB274406
ADB262090
ADB261103
ADB274372